

Final Report-Teratologic Evaluation of FDA 71-53 (Agar Agar) in Rabbits
9/17/73

Final Report-Teratologic Evaluation of FDA 71-53 (Agar Agar) in Mice, Rats &
7/31/73

JH

FROM



FOOD AND DRUG
Research LABORATORIES, INC.

ROUTE 17 (P.O. BOX 107)
WAVERLY, NEW YORK 14892

FINAL

July 31, 1973

#33

Teratologic Evaluation of FDA 71-53

(Agar Agar)

Mice, Rats, and Hamsters

MICE



**FOOD AND DRUG
Research LABORATORIES, INC.**

**F I N A L
R E P O R T**

WAVERLY DIVISION
Route 17
P.O. Box 107
Waverly, New York 14892
(607) 565-2931

Submitted to: DHEW/Public Health Service
Food and Drug Administration CA-272
5600 Fishers Lane-Room 5C-13
Rockville, Maryland 20852

Date July 31, 1973

Laboratory No. 1573 g
Contract No. FDA 71-260

Sample: Fine tan powdered material

Marking: FDA 71-53 (Agar agar)

Examination Requested: Teratologic evaluation of FDA 71-53 in mice.

Procedure: See Appendix I

Results: See Tables 1 through 4 and Appendix II

Conclusion:

See Following Page

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Kenneth Morgareidge
Kenneth Morgareidge, Ph.D.
Vice President



Conclusion

On the basis of the data presented herein, the following conclusion appears warranted:

"The administration of up to 329 mg/kg (body weight) of the test material to pregnant mice for 10 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The abnormalities seen in either soft or skeletal tissues of the test groups did not differ significantly from the number occurring spontaneously in the sham-treated controls.

However, at the highest level of administration (1570 mg/kg) there was a significant increase in mortality among treated dams and a decrease in the pregnancy rate of survivors. Of the females examined at term, there was a marked increase in the number of resorption sites, and live fetuses showed significant retardation in maturation (with lowered fetal weights).

It is to be noted that there was no clear evidence of a teratogenic effect of the test material even at the highest dose level. Furthermore, the type of finding seen is similar to that found previously in all of the high molecular weight polysaccharide substances tested in this series. It is the opinion of the investigator that the administration of what amounts to essentially an LD₅₀ dose (even though distributed over a 10-day period) had resulted in a predictable effect on both the pregnant animal and on the embryos present in the uterus."

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 261 & 262; 267 through 270

Material: FDA 71-53

Date: June 28, 1973

Laboratory No.: 1573 q

Table 1

Fate Summary
(Mice)

| Group | Material | Dose ** mg/kg | Total | | Surviving at Term Pregnant | |
|-------|-----------|------------------|-------|----------|-------------------------------|----------|
| | | | Mated | Pregnant | Total | Pregnant |
| 261 | Sham | 0.0 | 23 | 22 | 23 | 22 |
| 262 | Aspirin* | 150.0 | 28 | 20 | 28 | 20 |
| 267 | FDA 71-53 | 15.7 | 24 | 20 | 24 | 20 |
| 268 | FDA 71-53 | 72.9 | 25 | 23 | 25 | 23 |
| 269 | FDA 71-53 | 329.0 | 25 | 24 | 25 | 24 |
| 270 | FDA 71-53 | 1570.0 | 48 | 20 | 39 | 20 |

* Positive Control: 150.0 mg/kg

** Administered as a corn oil suspension (See Appendix I); 10 ml/kg of body weight

1) Includes all dams examined at term

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group: 261 & 262; 267 through 270Material: FDA 71-53Date: June 28, 1973Laboratory No. 1573 g

Table 2
Reproduction Data
(Mice)

| Group: | 261 | 262 | 267 | 268 | 269 | 270 |
|------------------------------------|------|-----------|------|------|-------|--------|
| Dose (mg/kg): | Sham | Aspirin** | 15.7 | 72.9 | 329.0 | 1570.0 |
| Pregnancies | | | | | | |
| Total No. | 22 | 20 | 20 | 23 | 24 | 20 |
| Died or Aborted (before Day 17) | 0 | 0 | 0 | 0 | 0 | 0 |
| To term (on Day 17) | 22 | 20 | 20 | 23 | 24 | 20 |
| Live Litters | | | | | | |
| Total No.* | 21 | 20 | 20 | 23 | 24 | 18 |
| Implant Sites | 258 | 247 | 221 | 284 | 292 | 239 |
| Total No. | 11.7 | 12.4 | 11.1 | 12.3 | 12.2 | 12.0 |
| Average/dam* | | | | | | |
| Resorptions | | | | | | |
| Total No.* | 19 | 15 | 4 | 14 | 13 | 51 |
| Dams with 1 or more sites resorbed | 8 | 10 | 4 | 9 | 7 | 14 |
| Dams with all sites resorbed | -- | -- | -- | -- | -- | 2 |
| Per cent partial resorptions | 36.4 | 50.0 | 20.0 | 39.1 | 29.2 | 70.0 |
| Per cent complete resorptions | -- | -- | -- | -- | -- | 10.0 |
| Live Fetuses | | | | | | |
| Total No. | 237 | 229 | 215 | 268 | 277 | 183 |
| Average/dam* | 10.8 | 11.5 | 10.8 | 11.7 | 11.5 | 9.15 |
| Sex ratio (M/F) | 0.68 | 0.75 | 0.76 | 0.80 | 0.73 | 0.72 |
| Dead Fetuses | | | | | | |
| Total* | 2 | 3 | 2 | 2 | 2 | 5 |
| Dams with 1 or more dead | 2 | 3 | 2 | 2 | 2 | 3 |
| Dams with all dead | -- | -- | -- | -- | -- | -- |
| Per cent partial dead | 9.09 | 15.0 | 10.0 | 8.69 | 8.33 | 15.0 |
| Per cent all dead | -- | -- | -- | -- | -- | -- |
| Average Fetus Weight, g | 0.91 | 0.79 | 0.86 | 0.91 | 0.90 | 0.73 |

* Includes only those dams examined at term.
** Positive Control: 150.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 261 & 262; 267 through 270Laboratory No. 1573 g

Table 3

Material FDA 71-53Date June 28, 1973Summary of Skeletal Findings*
(Mice)

| <u>Findings</u> | <u>Group No.:</u> | 261 | 262 | 267 | 268 | 269 | 270 |
|------------------------------------|----------------------|--------|-----------|--------|--------|--------|--------|
| | <u>Dose (mg/kg):</u> | Sham | Aspirin** | 15.7 | 72.9 | 329.0 | 1570.0 |
| Live Fetuses Examined (at term) | | 165/21 | 158/20 | 149/20 | 184/23 | 188/24 | 128/18 |
| Sternebrae | | | | | | | |
| Incomplete oss. | | 57/16 | 49/14 | 48/13 | 24/10 | 60/16 | 51/14 |
| Scrambled | | | | | | | |
| Bipartite | | 15/10 | 9/6 | 7/4 | 6/4 | 8/8 | 4/3 |
| Fused | | | | | | | |
| Extra | | | | 1/1 | | | |
| Missing | | 17/7 | 46/13 | 28/8 | 15/6 | 25/9 | 70/14 |
| Other | | | | | | | |
| Ribs | | | | | | | |
| Incomplete oss. | | | | | | | |
| Fused/split | | | | | | | |
| Wavy | | | | | | | |
| Less than 12 | | | | | | | |
| More than 13 | | 42/16 | 17/11 | 24/10 | 54/16 | 32/13 | 19/11 |
| Other | | | | | | | |
| Vertebrae | | | | | | | |
| Incomplete oss. | | 1/1 | 6/2 | 9/2 | 2/2 | 5/4 | 18/7 |
| Scrambled | | | | | | | |
| Fused | | | | | | | |
| Extra ctrs. oss. | | | | | | | |
| Scoliosis | | | 1/1 | | | | |
| Tail defects | | | | | | | |
| Other | | | | | | | |
| Skull | | | | | | | |
| Incomplete closure | | | | | | | |
| Missing | | | | | | | |
| Craniosostosis | | | | | | | |
| Other | | | | | | | |
| Extremities | | | | | | | |
| Incomplete oss. | | 1/1 | 5/2 | | 8/3 | 1/1 | 16/6 |
| Missing | | | | | | | |
| Extra | | | | | | | |
| Miscellaneous | | | | | | | |
| Hyoid; missing | | 25/8 | 40/13 | 49/14 | 23/9 | 34/9 | 53/14 |
| Hyoid; reduced | | 5/4 | 19/11 | 10/5 | 15/10 | 14/10 | 21/8 |

* Numerator=Number of fetuses affected; Denominator=Number of litters affected.

** Positive control: 150.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 261 & 262; 267 through 270Date June 28, 1973Material FDA 71-53Laboratory No. 1573 gTable 3-a
Summary of Soft Tissue Abnormalities
(Mice)

| Group | Material | Dose Level mg/kg | Dam | Number of Pups | Description |
|-------|-----------|---------------------|--------|-------------------|----------------------|
| 268 | FDA 71-53 | 72.9 | G 6036 | 1 | Umbilical Hernia |
| | | | G 3047 | 1 | Meningoencephalocele |
| | | | G 3049 | 1 | Hydrocephalus |
| 270 | FDA 71-53 | 1570.0 | G 3097 | 1 | Umbilical Hernia |

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 261 & 262; 267 through 270

Date June 28, 1973

Species Mice

Table 4

Laboratory No. 1573 g

Average Body Weights*

| Group | Material | Dose Level | Day----- | | | Day----- |
|-------|-----------|------------|----------|------|------|-----------|
| | | | 0 | 6 | 11 | |
| | mg/kg | | g | g | g | g |
| 261 | Sham | 0.0 | 27.5 | 31.3 | 34.6 | 43.0 |
| 262 | Aspirin** | 150.0 | 27.9 | 31.9 | 34.1 | 40.8 |
| 267 | FDA 71-53 | 15.7 | 26.1 | 29.6 | 33.9 | 40.8 |
| 268 | FDA 71-53 | 72.9 | 26.8 | 31.6 | 34.7 | 42.5 |
| 269 | FDA 71-53 | 329.0 | 28.1 | 31.7 | 34.7 | 42.5 |
| 270 | FDA 71-53 | 1570.0 | 27.0 | 31.9 | 31.7 | 35.9 |
| | | | | | | 40.6 (20) |

* Of pregnant dams

** Number of surviving dams in parentheses (c.f. Table 1)

*** Positive control: 150.0 mg/kg



Appendix I

Teratology Study in Mice

Virgin adult female albino CD-1 outbred mice were gang-housed in disposable plastic cages in temperature and humidity-controlled quarters with free access to food and fresh tap water. They were mated with young adult males, and observation of the vaginal sperm plug was considered Day 0 of gestation. Beginning on Day 6 and continuing daily through Day 15 of gestation, the females were dosed with the indicated dosages by oral intubation; the controls were sham treated.

Body weights were recorded on Days 0, 6, 11, 15, and 17 of gestation. All animals were observed daily for appearance and behavior with particular attention to food consumption and weight, in order to rule out any abnormalities which may have occurred as a result of anorexic effects in the pregnant female animal.

On Day 17 all dams were subjected to Caesarean section under surgical anesthesia, and the numbers of implantation sites, resorption sites, and live and dead fetuses were recorded. The body weights of the live pups were also recorded. The urogenital tract of each dam was examined in detail for anatomical normality.

All fetuses were examined grossly for the presence of external congenital abnormalities. One-third of the fetuses of each litter underwent detailed visceral examinations employing the Wilson technique. The remaining two-thirds were cleared in potassium hydroxide (KOH), stained with alizarin red S dye and examined for skeletal defects.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 261Material ShamDose 0.0 mg/kgDate June 28, 1973Laboratory No. 1573

Appendix II

Reproduction Data in Mice (Individual)

| Dam No. | Fate* | Implant Sites | Fetuses | | Sex M F | Resorption Sites | Average Fetus Weight (g) | Remarks |
|---------|-------|---------------|---------|------|-----------------|------------------|--------------------------|--------------|
| | | | Alive | Dead | | | | |
| S 3846 | P | 13 | 12 | | 4 | 8 | 1 | 0.83 |
| S 3847 | P | 11 | 11 | | 3 | 8 | | 0.93 |
| S 3848 | P | 6 | 6 | | 2 | 4 | | 0.75 |
| S 3849 | P | 11 | 11 | | 2 | 9 | | 0.97 |
| S 3850 | NP | 0 | | | | | | ---- |
| S 3851 | P | 13 | 13 | | 5 | 8 | | 0.89 |
| S 3852 | P | 13 | 13 | | 7 | 6 | | 0.72 |
| S 3853 | P | 12 | 12 | | 6 | 6 | | 0.88 |
| S 3854 | P | 12 | | 1 | 6 | 7 | 11 | ---- |
| S 3855 | P | 13 | 13 | | 6 | 5 | 2 | 0.91 |
| S 3856 | P | 13 | 11 | | 6 | 6 | | 1.02 |
| S 3857 | P | 12 | 12 | | 6 | 6 | | 0.91 |
| S 3858 | P | 13 | 13 | | 7 | 6 | | 0.92 |
| S 3859 | P | 7 | 7 | | 4 | 3 | | 1.18 |
| S 3860 | | | | | | | | Not Assigned |
| S 3861 | P | 12 | 11 | | 3 | 8 | 1 | 0.98 |
| S 3862 | P | 14 | 14 | | 7 | 7 | | 0.86 |
| S 3863 | P | 11 | 10 | | 4 | 6 | 1 | 1.09 |
| S 3864 | P | 14 | 12 | 1 | 6 | 6 | 1 | 0.98 |
| S 3865 | | | | | | | | Not Assigned |
| S 3866 | P | 11 | 11 | | 3 | 8 | | 0.90 |
| S 3867 | P | 12 | 11 | | 4 | 7 | 1 | 0.95 |
| S 3868 | P | 13 | 13 | | 5 | 8 | | 0.93 |
| S 3869 | P | 12 | 12 | | 4 | 8 | | 0.84 |
| S 3870 | P | 10 | 9 | | 2 | 7 | 1 | 0.72 |

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 262

Material Aspirin

Dose 150.0 mg/kg

Date June 28, 1973

Laboratory No. 1573

Appendix II

Reproduction Data in Mice (Individual)

| Dam No. | Fate* | Implant Sites | Fetuses | | Sex | | Resorption Sites | Average Fetus Weight (g) | Remarks |
|---------|-------|---------------|---------|------|-----|----|------------------|--------------------------|---------|
| | | | Alive | Dead | M | F | | | |
| A 3846 | P | 13 | 12 | 1 | 3 | 9 | 1 | 0.77 | |
| A 3847 | P | 11 | 10 | 1 | 4 | 6 | | 0.71 | |
| A 3848 | P | 10 | 10 | | 5 | 5 | | 0.89 | |
| A 3849 | NP | 0 | | | | | | ---- | |
| A 3850 | P | 15 | 15 | | 8 | 7 | | 0.76 | |
| A 3851 | P | 12 | 12 | | 5 | 7 | | 0.72 | |
| A 3852 | P | 13 | 12 | | 6 | 6 | 1 | 0.68 | |
| A 3853 | P | 12 | 12 | | 5 | 7 | | 0.69 | |
| A 3854 | NP | 0 | | | | | | ---- | |
| A 3855 | NP | 0 | | | | | | ---- | |
| A 3856 | NP | 0 | | | | | | ---- | |
| A 3857 | P | 12 | 12 | | 5 | 7 | | 0.80 | |
| A 3858 | P | 9 | 9 | | 3 | 6 | | 0.83 | |
| A 3859 | P | 13 | 12 | | 6 | 6 | 1 | 0.76 | |
| A 3860 | P | 14 | 13 | | 7 | 6 | 1 | 0.76 | |
| A 3861 | P | 12 | 10 | | 3 | 7 | 2 | 0.83 | |
| A 3862 | P | 12 | 11 | | 5 | 6 | 1 | 0.75 | |
| A 3863 | P | 11 | 11 | | 8 | 3 | | 1.01 | |
| A 3864 | P | 12 | 10 | | 3 | 7 | 2 | 0.87 | |
| A 3865 | NP | 0 | | | | | | ---- | |
| A 3866 | P | 11 | 10 | 1 | 7 | 3 | | 0.90 | |
| A 3867 | NP | 0 | | | | | | ---- | |
| A 3868 | P | 12 | 7 | 1 | 1 | 6 | 4 | 0.56 | |
| A 3869 | P | 14 | 14 | | 8 | 6 | | 0.86 | |
| A 3870 | NP | 0 | | | | | | ---- | |
| A 3871 | P | 14 | 13 | | 3 | 10 | 1 | 0.77 | |
| A 3872 | NP | 0 | | | | | | ---- | |
| A 3873 | P | 15 | 14 | | 3 | 11 | 1 | 0.91 | |

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 267
 Material FDA 71-53
 Dose 15.7 mg/kg

Date June 28, 1973
 Laboratory No. 1573 q

Appendix II

Reproduction Data in Mice

(Individual)

| Dam No. | Fate* | Implant Sites | Fetuses | | Sex M F | Resorption Sites | Average Fetus Weight (g) | Remarks |
|---------|-------|---------------|---------|------|---------------|---------------------|-----------------------------|--------------|
| | | | Alive | Dead | | | | |
| G 3001 | NP | 0 | | | | 1 | 5 | |
| G 3002 | P | 6 | 6 | | | | | 0.82 |
| G 3003 | NP | 0 | | | | | | ---- |
| G 3004 | NP | 0 | | | | | | ---- |
| G 3005 | P | 10 | 9 | | 4 | 5 | | 0.71 |
| G 3006 | P | 12 | 11 | | 6 | 5 | | 0.87 |
| G 3007 | P | 12 | 12 | | 4 | 8 | | 0.73 |
| G 3008 | P | 11 | 11 | | 5 | 6 | | 0.94 |
| G 3009 | P | 13 | 13 | | 5 | 8 | | 0.80 |
| G 3010 | P | 10 | 10 | | 5 | 5 | | 1.01 |
| G 3011 | P | 14 | 14 | | 6 | 8 | | 0.87 |
| G 3012 | P | 7 | 7 | | 4 | 3 | | 1.31 |
| G 3013 | P | 12 | 12 | | 5 | 7 | | 0.96 |
| G 3014 | P | 13 | 13 | | 6 | 7 | | 0.55 |
| G 3015 | | | | | | | 1 | Not Assigned |
| G 3016 | P | 8 | 7 | | 3 | 4 | | 0.87 |
| G 3017 | P | 11 | 11 | | 7 | 4 | | 0.83 |
| G 3018 | P | 12 | 12 | | 4 | 8 | | 0.72 |
| G 3019 | P | 14 | 13 | | 5 | 8 | | 0.82 |
| G 3020 | P | 9 | 8 | | 3 | 5 | | 1.01 |
| G 3021 | P | 13 | 13 | | 6 | 7 | | 0.76 |
| G 3022 | P | 13 | 12 | | 5 | 7 | | 0.86 |
| G 3023 | P | 11 | 11 | | 6 | 5 | | 0.89 |
| G 3024 | NP | 0 | | | | | | ---- |
| G 3025 | P | 10 | 10 | | 3 | 7 | | 0.91 |

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 268
 Material FDA 71-53
 Dose 72.9 mg/kg

Date June 28, 1973
 Laboratory No. 1573 g

Appendix II

Reproduction Data in Mice (Individual)

| Dam No. | Fate* | Implant Sites | Fetuses | | Sex M F | Resorption Sites | Average Fetus Weight (g) | Remarks |
|---------|-------|---------------|---------|------|---------------|---------------------|-----------------------------|---------|
| | | | Alive | Dead | | | | |
| G 3031 | P | 10 | 10 | | 4 | 6 | 1.00 | |
| G 3032 | P | 12 | 12 | | 4 | 8 | 0.90 | |
| G 3033 | P | 11 | 8 | | 3 | 5 | 0.86 | |
| G 3034 | P | 10 | 9 | | 4 | 5 | 0.88 | |
| G 3035 | P | 14 | 12 | | 5 | 7 | 1.00 | |
| G 3036 | P | 16 | 15 | | 7 | 8 | 0.77 | |
| G 3037 | P | 14 | 14 | | 7 | 7 | 0.87 | |
| G 3038 | P | 14 | 13 | | 6 | 7 | 0.84 | |
| G 3039 | P | 13 | 13 | | 5 | 8 | 0.86 | |
| G 3040 | P | 7 | 7 | | 3 | 4 | 1.63 | |
| G 3041 | P | 15 | 15 | | 6 | 9 | 0.98 | |
| G 3042 | P | 12 | 12 | | 5 | 7 | 0.86 | |
| G 3043 | P | 15 | 15 | | 7 | 8 | 0.89 | |
| G 3044 | P | 14 | 14 | | 4 | 10 | 0.96 | |
| G 3045 | P | 13 | 12 | 1 | 5 | 7 | 0.97 | |
| G 3046 | P | 11 | 9 | | 5 | 4 | 0.88 | |
| G 3047 | P | 12 | 11 | 1 | 4 | 7 | 0.65 | |
| G 3048 | P | 11 | 11 | | 4 | 7 | 0.92 | |
| G 3049 | P | 12 | 11 | | 4 | 7 | 0.72 | |
| G 3050 | P | 13 | 13 | | 7 | 6 | 0.85 | |
| G 3051 | P | 11 | 11 | | 6 | 5 | 0.89 | |
| G 3052 | P | 10 | 9 | | 6 | 3 | 0.88 | |
| G 3053 | P | 14 | 12 | | 8 | 4 | 1.00 | |
| G 3054 | NP | 0 | | | | | ---- | |
| G 3055 | NP | 0 | | | | | ---- | |

* P = Pregnant; NP = Not Pregnant

** Not all recorded.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 269
 Material FDA 71-53
 Dose 329.0 mg/kg

Appendix II

Reproduction Data in Mice

(Individual)

Date June 28, 1973Laboratory No. 1573 g

| Dam No. | Fate* | Implant Sites | Fetuses | | Sex M F | Resorption Sites | Average Fetus Weight (g) | Remarks |
|---------|-------|---------------|---------|------|---------------|------------------|--------------------------|---------|
| | | | Alive | Dead | | | | |
| G 3061 | P | 11 | 10 | 1 | 5 | 5 | 0.84 | |
| G 3062 | P | 10 | 10 | | 4 | 6 | 0.76 | |
| G 3063 | P | 13 | 13 | | 8 | 5 | 0.97 | |
| G 3064 | P | 16 | 16 | | 6 | 10 | 0.75 | |
| G 3065 | P | 9 | 9 | | 4 | 5 | 0.78 | |
| G 3066 | P | 13 | 12 | 1 | 4 | 8 | 1.15 | |
| G 3067 | P | 14 | 12 | | 4 | 8 | 0.94 | |
| G 3068 | P | 13 | 12 | | 3 | 9 | 0.98 | |
| G 3069 | P | 14 | 13 | 1 | 5 | 8 | 0.89 | |
| G 3070 | P | 10 | 9 | | 3 | 6 | 0.76 | |
| G 3071 | P | 13 | 13 | | 4 | 9 | 0.89 | |
| G 3072 | P | 12 | 9 | | 3 | 6 | 0.94 | |
| G 3073 | P | 12 | 12 | | 6 | 6 | 0.93 | |
| G 3074 | P | 15 | 15 | | 9 | 6 | 1.14 | |
| G 3075 | P | 10 | 10 | | 4 | 6 | 1.10 | |
| G 3076 | P | 11 | 11 | | 3 | 8 | 0.88 | |
| G 3077 | P | 11 | 11 | | 4 | 7 | 0.89 | |
| G 3078 | P | 13 | 13 | | 6 | 7 | 0.85 | |
| G 3079 | P | 12 | 12 | | 7 | 5 | 1.01 | |
| G 3080 | NP | 0 | | | | | ---- | |
| G 3081 | P | 10 | 10 | | 2 | 8 | 0.64 | |
| G 3082 | P | 13 | 9 | | 4 | 5 | 4 | 0.92 |
| G 3083 | P | 12 | 12 | | 7 | 5 | 0.84 | |
| G 3084 | P | 13 | 12 | | 7 | 5 | 1 | 0.81 |
| G 3085 | P | 12 | 12 | | 5 | 7 | 0.87 | |

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 270
 Material FDA 71-53
 Dose 1570.0 mg/kg

Date June 28, 1973
 Laboratory No. 1573 g

Appendix II

Reproduction Data in Mice (Individual)

| Dam No. | Pate* | Implant Sites | Fetuses Alive | Fetuses Dead | Sex M F | Resorption Sites | Average Fetus Weight (g) | Remarks |
|---------|-------|---------------|---------------|--------------|-----------------|------------------|--------------------------|-------------|
| G 3091 | NP | 0 | | | | | | ---- |
| G 3092 | NP | 0 | | | | | | ---- |
| G 3093 | NP | 0 | | | | | | ---- |
| G 3094 | NP | 0 | | | | | | ---- |
| G 3095 | | | | | | | | Died Day 12 |
| G 3096 | P | 14 | 12 | | | 14 | | ----- |
| G 3097 | P | 13 | | | | 3 | | 0.64 |
| G 3098 | | | | | | 9 | 1 | Died Day 11 |
| G 3099 | NP | 0 | | | | | | ---- |
| G 3100 | NP | 0 | | | | | | ---- |
| G 3101 | P | 15 | 15 | | | 7 | 8 | 0.57 |
| G 3102 | P | 13 | 12 | 1 | | 5 | 7 | 0.70 |
| G 3103 | P | 12 | 8 | 3 | | 3 | 5 | 0.73 |
| G 3104 | NP | 0 | | | | | | ---- |
| G 3105 | NP | 0 | | | | | | ---- |
| G 3106 | NP | 0 | | | | | | ---- |
| G 3107 | P | 11 | 8 | | | 4 | 4 | 0.70 |
| G 3108 | P | 13 | 13 | | | 6 | 7 | 0.57 |
| G 3109 | NP | 0 | | | | | | ---- |
| G 3110 | NP | 0 | | | | | | ---- |
| G 3111 | | | | | | | | Died Day 11 |
| G 3112 | NP | 0 | | | | | | ---- |
| G 3113 | | | | | | | | Died Day 13 |
| G 3114 | P | 13 | 12 | | | 8 | 4 | 1 |
| G 3115 | P | 13 | 11 | | | 5 | 6 | 2 |
| G 3116 | P | 11 | 9 | | | 3 | 6 | 2 |
| G 3117 | NP | 0 | | | | | | 0.82 |

Continued on next page.

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 270
 Material FDA 71-53
 Dose 1570.0 mg/kg

Date June 28, 1973
 Laboratory No. 1573 q

Appendix II

Reproduction Data in Mice
 (Individual)

| Dam No. | Fate* | Implant Sites | Alive | Fetuses Dead | Sex M F | Resorption Sites | Average Fetus Weight (g) | Remarks |
|-----------|-------|---------------|-------|--------------|---------------|---------------------|-----------------------------|--------------|
| Continued | | | | | | | | |
| G 3118 | P | | 8 | | | 8 | | |
| G 3119 | P | | 13 | 12 | 6 4 | 6 8 | | 0.83 0.82 |
| G 3120 | P | | 12 | 12 | | | | |
| G 3121 | | | | | | | | Died Day 9 |
| G 3122 | NP | 0 | | | | | | |
| G 3123 | | | | | | | | |
| G 3124 | P | | 12 | 11 | 4 | 7 | 1 | 0.62 |
| G 3125 | P | | 12 | 11 | 4 | 7 | 1 | 0.82 |
| G 3126 | P | | 15 | 15 | 5 | 10 | | 0.64 |
| G 3127 | NP | 0 | | | | | | |
| G 3128 | NP | 0 | | | | | | |
| G 3129 | P | | 6 | 4 | 3 | 1 | 2 | 0.82 |
| G 3130 | NP | 0 | | | | | | |
| G 3131 | | | | | | | | |
| G 3132 | P | | 12 | 4 | 1 | 2 | 7 | 0.48 |
| G 3133 | | | | | | | | |
| G 3134 | NP | 0 | | | | | | |
| G 3135 | P | | 13 | 6 | 2 | 4 | 7 | 0.71 |
| G 3136 | | | | | | | | |
| G 3137 | P | | 8 | 8 | 3 | 5 | | 0.86 |
| G 3138 | NP | 0 | | | | | | |

* P = Pregnant; NP = Not Pregnant

R A T S



**FOOD AND DRUG
Research LABORATORIES, INC.**

**F I N A L
R E P O R T**

WAVERLY DIVISION
Route 17
P.O. Box 107
Waverly, New York 14892
(607) 565-2931

Submitted to: DHEW/Public Health Service
Food and Drug Administration CA-272
5600 Fishers Lane-Room 5C-13
Rockville, Maryland 20852

Date July 31, 1973

Laboratory No. 1574 g
Contract No. FDA 71-260

Sample: Fine tan powdered material

Marking: FDA 71-53 (Agar Agar)

Examination Requested: Teratologic evaluation of FDA 71-53 in rats

Procedure: See Appendix I

Results: See Tables 1 through 4 and Appendix II

Conclusion:

On the basis of the data presented herein, the following conclusion appears to be warranted:

"The administration of up to 1140 mg/kg (body weight) of the test material to pregnant rats for 10 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls."

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Kenneth Morgareidge
Kenneth Morgareidge Ph.D.
Vice President

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 261 & 262; 267 through 270

Material: FDA 71-53

Date: June 28, 1973

Laboratory No.: 1574 q

Table 1

Fate Summary
(Rats)

| Group | Material | Dose ** mg/kg | Mated | Total | Surviving at Term | |
|-------|-----------|------------------|-------|-------|-------------------|----------------|
| | | | | | Pregnant | Total Pregnant |
| 261 | Sham | 0.0 | 25 | 23 | 25 | 23 |
| 262 | Aspirin* | 250.0 | 25 | 25 | 25 | 25 |
| 267 | FDA 71-53 | 11.4 | 25 | 21 | 25 | 21 |
| 268 | FDA 71-53 | 53.0 | 25 | 22 | 25 | 22 |
| 269 | FDA 71-53 | 247.0 | 25 | 21 | 25 | 21 |
| 270 | FDA 71-53 | 1140.0 | 25 | 24 | 25 | 24 |

* Positive Control: 250.0 mg/kg

** Administered as a corn oil suspension (See Appendix I)

1) Includes all dams examined at term

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group: 261 & 262; 267 through 270Material: FDA 71-53Date: June 28, 1973

Table 2
Reproduction Data
(Rats)
Laboratory No. 1574 g

| Group: | 261 | 262 | 267 | 268 | 269 | 270 |
|------------------------------------|------|-----------|------|------|-------|--------|
| Dose (mg/kg): | Sham | Aspirin** | 11.4 | 53.0 | 247.0 | 1140.0 |
| Pregnancies | | | | | | |
| Total No. | 23 | 25 | 21 | 22 | 21 | 24 |
| Died or Aborted (before Day 20) | 0 | 0 | 0 | 0 | 0 | 0 |
| To term (on Day 20) | 23 | 25 | 21 | 22 | 21 | 24 |
| Live Litters | | | | | | |
| Total No.* | 23 | 24 | 21 | 22 | 21 | 24 |
| Implant Sites | | | | | | |
| Total No. | 272 | 256 | 244 | 232 | 261 | 268 |
| Average/dam* | 11.8 | 10.2 | 11.6 | 10.5 | 12.4 | 11.2 |
| Resorptions | | | | | | |
| Total No.* | 1 | 26 | 8 | --- | 6 | 3 |
| Dams with 1 or more sites resorbed | 1 | 13 | 5 | --- | 4 | 2 |
| Dams with all sites resorbed | -- | 1 | -- | --- | -- | -- |
| Per cent partial resorptions | 4.35 | 52.0 | 23.8 | -- | 19.0 | 8.33 |
| Per cent complete resorptions | -- | 4.00 | -- | --- | -- | -- |
| Live Fetuses | | | | | | |
| Total No. | 271 | 229 | 236 | 232 | 255 | 265 |
| Average/dam* | 11.8 | 9.16 | 11.2 | 10.5 | 12.1 | 11.0 |
| Sex ratio (M/F) | 0.91 | 0.79 | 0.76 | 0.77 | 0.71 | 0.86 |
| Dead Fetuses | | | | | | |
| Total* | -- | 1 | -- | --- | -- | -- |
| Dams with 1 or more dead | -- | 1 | -- | --- | -- | -- |
| Dams with all dead | -- | -- | -- | --- | -- | -- |
| Per cent partial dead | -- | 4.00 | -- | --- | -- | -- |
| Per cent all dead | -- | -- | -- | --- | -- | -- |
| Average Fetus Weight, g | 3.79 | 2.51 | 3.84 | 4.02 | 3.95 | 3.90 |

* Includes only those dams examined at term.
** Positive Control: 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 261 & 262; 267 through 270Laboratory No. 1574 g

Table 3

Material FDA 71-53Date June 28, 1973Summary of Skeletal Findings*
(Rats)

| Findings | Group No.: | 261 | 262 | 267 | 268 | 269 | 270 |
|------------------------------------|---------------|--------|-----------|--------|--------|--------|--------|
| | Dose (mg/kg): | Sham | Aspirin** | 11.4 | 53.0 | 247.0 | 1140.0 |
| Live Fetuses Examined (at term) | | 190/23 | 162/24 | 164/21 | 164/22 | 176/21 | 184/24 |
| Sternebrae | | | | | | | |
| Incomplete oss. | 100/20 | 113/24 | | 48/14 | 44/14 | 79/19 | 62/20 |
| Scrambled | | | | | | | |
| Bipartite | 1/1 | 7/7 | | 1/1 | 3/3 | 4/4 | 1/1 |
| Fused | | | | | | | |
| Extra | | | | | | | |
| Missing | 9/6 | 132/24 | | 4/3 | 3/3 | 11/2 | 9/4 |
| Other | | | | | | | |
| Ribs | | | | | | | |
| Incomplete oss. | | | 3/3 | | 1/1 | 4/2 | |
| Fused/split | | | 5/3 | | | | |
| Wavy | 9/6 | 68/20 | | 16/9 | 18/11 | 17/8 | 23/13 |
| Less than 12 | | | | | | | |
| More than 13 | 1/1 | 126/24 | | 1/1 | | | 2/1 |
| Other | | | | | | | |
| Vertebrae | | | | | | | |
| Incomplete oss. | 6/4 | 142/24 | | 15/7 | 15/8 | 10/4 | 11/6 |
| Scrambled | | | | | | | |
| Fused | | | | | | | |
| Extra ctrs. oss. | | | | | | | |
| Scoliosis | | | | | | | |
| Tail defects | | | | | | | |
| Other; Hyoid, bipartite | | | | | | 1/1 | |
| Skull | | | | | | | |
| Incomplete closure | 40/13 | 104/23 | | 20/10 | 27/13 | 49/17 | 25/13 |
| Missing | | 2/2 | | | | | |
| Craniostosis | | | | | | | |
| Other | | | | | | | |
| Extremities | | | 6/3 | | | | |
| Incomplete oss. | | | | | | | |
| Missing | | | | | | | |
| Extra | | | | | | | |
| Miscellaneous | | | | | | | |
| Hyoid; missing | 19/10 | 76/23 | | 15/8 | 23/11 | 20/10 | 16/13 |
| Hyoid; reduced | 26/13 | 24/13 | | 10/5 | 10/5 | 11/8 | 27/14 |

* Numerator=Number of fetuses affected; Denominator=Number of litters affected.

** Positive control: 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 261 & 262; 267 through 270Date June 28, 1973Material FDA 71-53Laboratory No. 1574 q

Table 3-a
Summary of Soft Tissue Abnormalities
(Rats)

| Group | Material | Dose Level mg/kg | Dam | Number of Pups | Description |
|-------|-----------|---------------------|--------|-------------------|---|
| 262 | Aspirin* | 250.0 | A 4846 | 1 | Encephalomyelocele |
| | | | A 4851 | 1 | Meningoencephalocele |
| | | | A 4855 | 1 | Encephalomyelocele; umbilical hernia |
| | | | A 4860 | 1 | Umbilical hernia |
| 267 | FDA 71-53 | 11.4 | G 4008 | 1 | Gastrocele |

* Positive Control: 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 261 & 262; 267 through 270

Date June 28, 1973

Species Rats

Laboratory No. 1574 g

Table 4

Average Body Weights*

| Group | Material | Dose Level | 0 | 6 | 11 | 15 | 20** |
|-------|------------|------------|-----|-----|-----|-----|----------|
| | | mg/kg | | | | | g |
| 261 | Sham | 0.0 | 223 | 244 | 255 | 280 | 344 (23) |
| 262 | Aspirin*** | 250.0 | 215 | 231 | 245 | 260 | 309 (25) |
| 267 | FDA 71-53 | 11.4 | 229 | 248 | 266 | 290 | 356 (21) |
| 268 | FDA 71-53 | 53.0 | 216 | 231 | 248 | 268 | 329 (22) |
| 269 | FDA 71-53 | 247.0 | 232 | 250 | 267 | 288 | 355 (21) |
| 270 | FDA 71-53 | 1140.0 | 220 | 236 | 250 | 271 | 323 (24) |

* Of pregnant dams

** Number of surviving dams in parentheses (c.f. Table 1)

*** Positive control: 250.0 mg/kg



Appendix I

Teratology Study in Rats

Virgin adult female albino rats (Wistar derived stock) were individually housed in mesh bottom cages in temperature and humidity-controlled quarters with free access to food and fresh tap water. They were mated with young adult males, and observation of the vaginal sperm plug was considered Day 0 of gestation. Beginning on Day 6 and continuing daily through Day 15 of gestation, the females were dosed with the indicated dosages by oral intubations. The controls were sham treated with the vehicle at a level equivalent to the group receiving the highest test dose. The test material was prepared and doses calculated according to the following table:

| Dosage (mg/kg) | Dose (ml/kg) | Concentration (mg/ml) |
|-------------------|-----------------|--------------------------|
| ≤ 250 | 1 | ≤ 250 |
| 251 - 500 | 2 | 125 - 250 |
| 501 - 750 | 3 | .133 - 250 |
| 751 - 1000 | 4 | 187 - 250 |
| 1001 - 1250 | 5 | 200 - 250 |
| 1251 - 1500 | 6 | 208 - 250 |
| 1501 - 1600 | 6.4 | 235 - 250 |

Body weights were recorded on Days 0, 6, 11, 15, and 20 of gestation. All animals were observed daily for appearance and behavior with particular attention to food consumption and weight, in order to rule out any abnormalities which may have occurred as a result of anorexic effects in the pregnant female animal.

On Day 20 all dams were subjected to Caesarean section under surgical anesthesia, and the numbers of implantation sites, resorption sites, and live and dead fetuses were recorded. The body weights of



the live pups were also recorded. The urogenital tract of each dam was examined in detail for anatomical normality.

All fetuses were examined grossly for the presence of external congenital abnormalities. One-third of the fetuses of each litter underwent detailed visceral examinations employing the Wilson technique. The remaining two-thirds were cleared in potassium hydroxide (KOH), stained with alizarin red S dye and examined for skeletal defects.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 261
 Material Sham
 Dose 0.0 mg/kg

Appendix II

Date June 28, 1973
 Laboratory No. 1574

Reproduction Data in Rats (Individual)

| Dam No. | Fate* | Implant Sites | Fetuses | | Sex M F | Resorption Sites | Average Fetus Weight (g) | Remarks |
|---------|-------|---------------|---------|------|---------------|---------------------|-----------------------------|---------|
| | | | Alive | Dead | | | | |
| S 4846 | P | 10 | 10 | | 4 | 6 | 3.89 | |
| S 4847 | P | 13 | 13 | | 5 | 8 | 3.75 | |
| S 4848 | P | 9 | 9 | | -** | -** | 3.52 | |
| S 4849 | P | 5 | 5 | | 2 | 3 | 3.53 | |
| S 4850 | NP | 0 | | | --- | --- | --- | |
| S 4851 | P | 11 | 11 | | 3 | 8 | 4.47 | |
| S 4852 | P | 10 | 10 | | 5 | 5 | 3.87 | |
| S 4853 | P | 14 | 14 | | 6 | 8 | 3.83 | |
| S 4854 | P | 20 | 19 | | 6 | 13 | 1 | 4.09 |
| S 4855 | P | 15 | 15 | | 2 | 13 | | 3.44 |
| S 4856 | P | 12 | 12 | | 9 | 3 | | 3.99 |
| S 4857 | P | 14 | 14 | | 8 | 6 | | 3.80 |
| S 4858 | P | 12 | 12 | | 4 | 8 | | 4.00 |
| S 4859 | P | 13 | 13 | | 9 | 4 | | 3.67 |
| S 4860 | P | 11 | 11 | | 7 | 4 | | 3.84 |
| S 4861 | P | 8 | 8 | | 6 | 2 | | 3.61 |
| S 4862 | P | 14 | 14 | | 6 | 8 | | 3.77 |
| S 4863 | P | 10 | 10 | | 5 | 5 | | 3.57 |
| S 4864 | P | 15 | 15 | | 4 | 11 | | 3.64** |
| S 4865 | P | 13 | 13 | | 8 | 5 | | 3.85 |
| S 4866 | NP | 0 | | | --- | --- | --- | |
| S 4867 | P | 11 | 11 | | 9 | 2 | | 3.72 |
| S 4868 | P | 11 | 11 | | 5 | 6 | | 4.11 |
| S 4869 | P | 12 | 12 | | 6 | 6 | | 3.43 |
| S 4870 | P | 9 | 9 | | 6 | 3 | | 3.69 |

* P = Pregnant; NP = Not Pregnant

** Not all recorded. (Average of 14 fetuses)

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 262Material AspirinDose 250.0 mg/kgDate June 28, 1973Laboratory No. 1574

Appendix II

Reproduction Data in Rats (Individual)

| Dam No. | Fate* | Implant Sites | Fetuses | | Sex | | Resorption M F | Average Fetus Weight (g) | Remarks |
|---------|-------|---------------|---------|------|-----|----|-------------------|--------------------------|---------|
| | | | Alive | Dead | M | F | | | |
| A 4846 | P | 11 | 11 | | 4 | 7 | | | 2.77 |
| A 4847 | P | 16 | 15 | | 9 | 6 | | | 2.33 |
| A 4848 | P | 8 | 8 | | 4 | 4 | | | 2.57 |
| A 4849 | P | 8 | 8 | | 3 | 5 | | | 2.16 |
| A 4850 | P | 12 | 12 | | 4 | 8 | | | 2.76 |
| A 4851 | P | 10 | 7 | | 2 | 5 | | | 2.33 |
| A 4852 | P | 2 | 2 | | 0 | 2 | | | 2.35 |
| A 4853 | P | 13 | 12 | | 9 | 3 | | | 2.63 |
| A 4854 | P | 9 | 9 | | 2 | 7 | | | 2.42 |
| A 4855 | P | 10 | 3 | | 0 | 3 | | | 2.18 |
| A 4856 | P | 10 | 10 | | 0 | 10 | | | 2.89 |
| A 4857 | P | 9 | 8 | | 4 | 4 | | | 2.44 |
| A 4858 | P | 12 | 11 | | 5 | 6 | | | 2.51 |
| A 4859 | P | 1 | | | | | | | --- |
| A 4860 | P | 9 | 7 | | 4 | 3 | | | 2.38 |
| A 4861 | P | 12 | 12 | | 7 | 5 | | | 3.10 |
| A 4862 | P | 13 | 13 | | 4 | 9 | | | 2.46 |
| A 4863 | P | 11 | 9 | | 5 | 4 | | | 1.95 |
| A 4864 | P | 10 | 10 | | 4 | 6 | | | 2.39 |
| A 4865 | P | 11 | 8 | | 3 | 5 | | | 2.45 |
| A 4866 | P | 12 | 12 | | 7 | 5 | | | 3.18 |
| A 4867 | P | 12 | 11 | | 5 | 6 | | | 2.10 |
| A 4868 | P | 11 | 9 | | 4 | 5 | | | 2.33 |
| A 4869 | P | 12 | 12 | | 5 | 7 | | | 3.12 |
| A 4870 | P | 10 | 7 | | 3 | 2 | | | 2.43 |

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 267Material FDA 71-53Dose 11.4 mg/kgDate June 28, 1973Laboratory No. 1574 g

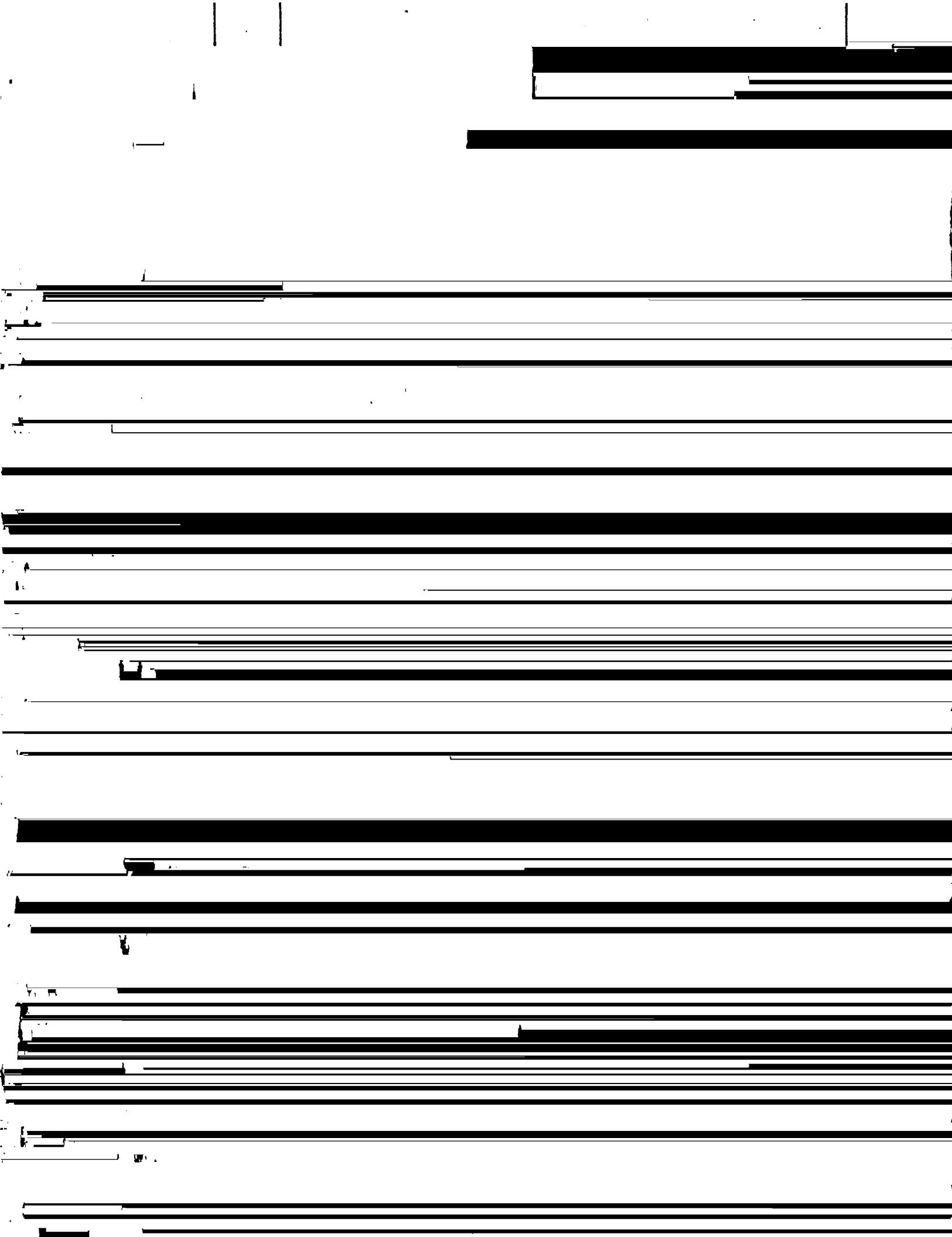
Appendix II

Reproduction Data in Rats

(Individual)

| Dam No. | Fate* | Implant Sites | Fetuses | | Sex M F | Resorption Sites | Average Fetus Weight (g) | Remarks |
|---------|-------|---------------|---------|------|---------------|---------------------|-----------------------------|---------|
| | | | Alive | Dead | | | | |
| G 4001 | P | 13 | 13 | | 3 | 10 | | 3.78 |
| G 4002 | P | 11 | 11 | | 4 | 7 | | 3.81 |
| G 4003 | P | 14 | 14 | | 8 | 6 | | 3.73 |
| G 4004 | NP | 0 | | | | | | --- |
| G 4005 | P | 11 | 11 | | 4 | 7 | | 3.87 |
| G 4006 | P | 12 | 10 | | 5 | 5 | 2 | 3.61 |
| G 4007 | P | 12 | 12 | | 5 | 7 | | 3.95 |
| G 4008 | P | 16 | 16 | | 6 | 10 | | 3.97 |
| G 4009 | P | 11 | 10 | | 3 | 7 | 1 | 3.63 |
| G 4010 | NP | 0 | | | | | | --- |
| G 4011 | P | 11 | 11 | | 6 | 5 | | 3.84 |
| G 4012 | P | 6 | 6 | | 2 | 4 | | 4.05 |
| G 4013 | P | 10 | 7 | | 5 | 2 | 3 | 3.98 |
| G 4014 | P | 10 | 9 | | 5 | 4 | 1 | 4.01 |
| G 4015 | NP | 0 | | | | | | --- |
| G 4016 | P | 11 | 11 | | 5 | 6 | | 4.03 |
| G 4017 | P | 13 | 13 | | 6 | 7 | | 3.16 |
| G 4018 | P | 11 | 11 | | 7 | 4 | | 4.19 |
| G 4019 | NP | 0 | | | | | | --- |
| G 4020 | P | 14 | 14 | | 7 | 7 | | 4.21 |
| G 4021 | P | 9 | 9 | | 4 | 5 | | 3.42 |
| G 4022 | P | 13 | 12 | | 1 | 11 | 1 | 3.90 |
| G 4023 | P | 13 | 13 | | 5 | 8 | | 3.67 |
| G 4024 | P | 14 | 14 | | 7 | 7 | | 3.83 |
| G 4025 | P | 9 | 9 | | 4 | 5 | | 4.04 |

* P = Pregnant; NP = Not Pregnant



FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 269Material FDA 71-53Dose 24.0 mg/kgDate June 28, 1973Laboratory No. 15749

Appendix II

Reproduction Data in Rats

(Individual)

Dam No. Fate*

Implant Sites

Fetuses

Reproduction Data in Rats

(Individual)

| Dam No. | Fate* | Implant Sites | Fetuses | | Sex M F | Resorption Sites | Average Fetus Weight (g) | Remarks |
|---------|-------|---------------|---------|------|---------------|---------------------|-----------------------------|---------|
| | | | Alive | Dead | | | | |
| G 4061 | P | 12 | 12 | | 5 | 7 | | 4.07 |
| G 4062 | P | 11 | 10 | | 2 | 8 | 1 | 3.69 |
| G 4063 | P | 13 | 13 | | 5 | 8 | | 3.94 |
| G 4064 | NP | 0 | | | | | | ---- |
| G 4065 | NP | 0 | | | | | | ---- |
| G 4066 | P | 14 | 14 | | 7 | 7 | | 3.99 |
| G 4067 | P | 16 | 16 | | 8 | 8 | | 4.01 |
| G 4068 | P | 9 | 6 | | 1 | 5 | 3 | 4.00 |
| G 4069 | P | 13 | 13 | | 4 | 9 | | 3.30 |
| G 4070 | P | 10 | 9 | | 5 | 4 | 1 | 3.84 |
| G 4071 | P | 13 | 13 | | 7 | 6 | | 3.89 |
| G 4072 | NP | 0 | | | | | | ---- |
| G 4073 | P | 12 | 12 | | 5 | 7 | | 4.27 |
| G 4074 | P | 14 | 14 | | 6 | 8 | | 3.85 |
| G 4075 | P | 17 | 16 | | 8 | 8 | 1 | 3.87 |
| G 4076 | P | 10 | 10 | | 3 | 7 | | 4.23 |
| G 4077 | NP | 0 | | | | | | ---- |
| G 4078 | P | 14 | 14 | | 6 | 8 | | 3.79 |
| G 4079 | P | 12 | 12 | | 5 | 7 | | 4.13 |
| G 4080 | P | 10 | 10 | | 3 | 7 | | 3.92 |
| G 4081 | P | 12 | 12 | | 7 | 5 | | 3.93 |
| G 4082 | P | 15 | 15 | | 7 | 8 | | 4.05 |
| G 4083 | P | 8 | 8 | | 1 | 7 | | 3.74 |
| G 4084 | P | 15 | 15 | | 9 | 6 | | 4.39 |
| G 4085 | P | 11 | 11 | | 2 | 9 | | 4.08 |

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 270Material FDA 71-53Dose 1140.0 mg/kgDate June 28, 1973Laboratory No. 1574 g

Appendix II

Reproduction Data in Rats

(Individual)

| Dam No. | Fate* | Implant Sites | Fetuses | | Sex | | Resorption Sites | Average Fetus Weight (g) | Remarks |
|---------|-------|---------------|---------|------|-----|---|------------------|--------------------------|---------|
| | | | Alive | Dead | M | F | | | |
| G 4091 | P | 12 | 12 | | 5 | 7 | | 3.82 | |
| G 4092 | P | 11 | 11 | | 4 | 7 | | 3.81 | |
| G 4093 | P | 11 | 11 | | 3 | 8 | | 3.48 | |
| G 4094 | P | 12 | 12 | | 3 | 9 | | 3.84 | |
| G 4095 | P | 12 | 12 | | 4 | 8 | | 3.74 | |
| G 4096 | P | 9 | 9 | | 2 | 7 | | 4.21 | |
| G 4097 | P | 10 | 10 | | 7 | 3 | | 3.52 | |
| G 4098 | P | 13 | 13 | | 4 | 9 | | 4.14 | |
| G 4099 | P | 8 | 8 | | 1 | 7 | | 3.92 | |
| G 4100 | P | 10 | 10 | | 5 | 5 | | 3.80 | |
| G 4101 | P | 12 | 12 | | 3 | 9 | | 3.70 | |
| G 4102 | P | 13 | 13 | | 7 | 6 | | 3.92 | |
| G 4103 | P | 12 | 12 | | 8 | 4 | | 3.88 | |
| G 4104 | NP | 0 | | | | | | ---- | |
| G 4105 | P | 7 | 7 | | 3 | 4 | | 4.00 | |
| G 4106 | P | 15 | 13 | | 5 | 8 | 2 | 3.93 | |
| G 4107 | P | 10 | 9 | | 5 | 4 | 1 | 3.88 | |
| G 4108 | P | 4 | 4 | | 1 | 3 | | 4.66 | |
| G 4109 | P | 10 | 10 | | 6 | 4 | | 3.94 | |
| G 4110 | P | 15 | 15 | | 10 | 5 | | 3.30 | |
| G 4111 | P | 11 | 11 | | 7 | 4 | | 3.74 | |
| G 4112 | P | 11 | 11 | | 8 | 3 | | 3.89 | |
| G 4113 | P | 14 | 14 | | 8 | 6 | | 3.98 | |
| G 4114 | P | 12 | 12 | | 7 | 5 | | 4.69 | |
| G 4115 | P | 14 | 14 | | 7 | 7 | | 3.84 | |

* P = Pregnant; NP = Not Pregnant

HANS TELES



**FOOD AND DRUG
Research LABORATORIES, INC.**

**F I N A L
R E P O R T**

WAVERLY DIVISION
Route 17
P.O. Box 107
Waverly, New York 14892
(607) 565-2931

Submitted to: DHEW/Public Health Service
Food and Drug Administration CA-272
5600 Fishers Lane-Room 5C-13
Rockville, Maryland 20852

Date July 31, 1973

Laboratory No. 1575 g
Contract No. FDA 71-260

Sample: Fine tan powdered material

Marking: FDA 71-53 (Agar Agar)

Examination Requested: Teratologic evaluation of FDA 71-53 in hamsters

Procedure: See Appendix I

Results: See Tables 1 through 4 and Appendix II

Conclusion:

On the basis of the data presented herein, the following conclusion appears to be warranted:

"The administration of up to 650 mg/kg (body weight) of the test material to pregnant hamsters for 5 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls."

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Kenneth Morgareidge

Kenneth Morgareidge, Ph.D.
Vice President

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 261 & 262; 267 through 270Date: June 28, 1973Material: FDA 71-53Laboratory No.: 1575 q

Table 1

Fate Summary
(Hamsters)

| Group | Material | Dose ** mg/kg | Mated | Total | Pregnant | Surviving at Term | |
|-------|-----------|------------------|-------|-------|----------|-------------------|----------|
| | | | | | | Total | Pregnant |
| 261 | Sham | 0.0 | 27 | 22 | 22 | 27 | 22 |
| 262 | Aspirin* | 250.0 | 27 | 22 | 22 | 27 | 22 |
| 267 | FDA 71-53 | 6.5 | 30 | 27 | 27 | 29 | 26 |
| 268 | FDA 71-53 | 30.2 | 25 | 23 | 23 | 24 | 22 |
| 269 | FDA 71-53 | 140.3 | 25 | 24 | 24 | 25 | 24 |
| 270 | FDA 71-53 | 650.0 | 29 | 24 | 24 | 29 | 24 |

* Positive Control: 250.0 mg/kg

** Administered as a corn oil suspension (See Appendix I)

1) Includes all dams examined at term

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group: 261 & 262; 267 through 270Material: FDA 71-53Date: June 28, 1973Laboratory No. 1575 g

Table 2

Reproduction Data
(Hamsters)

| Group: | 261 | 262 | 267 | 268 | 269 | 270 |
|------------------------------------|------|-----------|------|------|-------|-------|
| Dose (mg/kg): | Sham | Aspirin** | 6.5 | 30.2 | 140.3 | 650.0 |
| Pregnancies | | | | | | |
| Total No. | 22 | 22 | 27 | 23 | 24 | 24 |
| Died or Aborted (before Day 14) | 0 | 0 | 1 | 1 | 0 | 0 |
| To term (on Day 14) | 22 | 22 | 26 | 22 | 24 | 24 |
| Live Litters | | | | | | |
| Total No.* | 21 | 22 | 26 | 22 | 24 | 24 |
| Implant Sites | | | | | | |
| Total No. | 308 | 298 | 342 | 312 | 311 | 329 |
| Average/dam* | 14.0 | 13.6 | 13.2 | 14.2 | 13.0 | 13.7 |
| Resorptions | | | | | | |
| Total No.* | 9 | 6 | 11 | 8 | 6 | 9 |
| Dams with 1 or more sites resorbed | 7 | 4 | 8 | 5 | 5 | 5 |
| Dams with all sites resorbed | -- | -- | -- | -- | -- | -- |
| Per cent partial resorptions | 31.8 | 18.2 | 30.8 | 22.7 | 20.8 | 20.8 |
| Per cent complete resorptions | -- | -- | -- | -- | -- | -- |
| Live Fetuses | | | | | | |
| Total No. | 283 | 292 | 326 | 303 | 304 | 319 |
| Average/dam* | 12.9 | 13.2 | 12.5 | 13.8 | 12.7 | 13.3 |
| Sex ratio (M/F) | 0.68 | 0.67 | 0.66 | 0.62 | 0.62 | 0.70 |
| Dead Fetuses | | | | | | |
| Total* | 16 | -- | 5 | 1 | 1 | 1 |
| Dams with 1 or more dead | 1 | -- | 1 | 1 | 1 | 1 |
| Dams with all dead | -- | -- | -- | -- | -- | -- |
| Per cent partial dead | 4.55 | -- | 3.85 | 4.55 | 4.17 | 4.17 |
| Per cent all dead | -- | -- | -- | -- | -- | -- |
| Average Fetus Weight, g | 1.80 | 1.80 | 1.81 | 1.82 | 1.92 | 1.84 |

* Includes only those dams examined at term.
** Positive Control: 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 261 & 262; 267 through 270Laboratory No. 1575 g

Table 3

Material FDA 71-53Date June 28, 1973Summary of Skeletal Findings*
(Hamsters)

| <u>Findings</u> | <u>Group No.:</u> | 261 | 262 | 267 | 268 | 269 | 270 |
|------------------------------------|----------------------|--------|-----------|--------|--------|--------|--------|
| | <u>Dose (mg/kg):</u> | Sham | Aspirin** | 6.5 | 30.2 | 140.3 | 650.0 |
| Live Fetuses Examined (at term) | | 196/21 | 203/22 | 225/26 | 208/22 | 214/24 | 223/24 |
| Sternebrae | | | | | | | |
| Incomplete oss. | | 89/18 | 102/20 | 85/24 | 87/20 | 75/17 | 49/17 |
| Scrambled | | | | | | | |
| Bipartite | | 17/13 | 27/15 | 18/13 | 16/12 | 14/8 | 19/11 |
| Fused | | 1/1 | | | | | |
| Extra | | 19/7 | 8/5 | | 9/6 | 24/10 | 3/3 |
| Missing | | 26/10 | 18/10 | 23/6 | 32/9 | 6/5 | 25/8 |
| Other | | | | | | | |
| Ribs | | | | | | | |
| Incomplete oss. | | | | | | | |
| Fused/split | | | 2/2 | | | 2/1 | |
| Wavy | | 1/1 | | | | | |
| Less than 12 | | | | | | | |
| More than 13 | | 83/18 | 55/19 | 53/19 | 70/20 | 68/22 | 49/19 |
| Other | | | | | | | |
| Vertebrae | | | | | | | |
| Incomplete oss. | | 1/1 | 2/2 | 2/2 | 5/4 | 2/2 | |
| Scrambled | | | | | | | |
| Fused | | | | | | | |
| Extra ctrs. oss. | | | | | | | |
| Scoliosis | | | | | | | |
| Tail defects | | | | | | | |
| Other | | | | | | | |
| Skull | | | | | | | |
| Incomplete closure | | | | | | | |
| Missing | | | | | | | |
| Craniostosis | | | | | | | |
| Other | | | | | | | |
| Extremities | | | | | | | |
| Incomplete oss. | | 2/2 | 1/1 | 4/3 | 4/3 | 1/1 | 11/2 |
| Missing | | | | | | | |
| Extra | | | | | | | |
| Miscellaneous | | | | | | | |
| Hyoid; missing | | | 2/2 | 3/2 | 2/2 | 1/1 | 11/2 |
| Hyoid; reduced | | 8/6 | 9/5 | 2/2 | 9/6 | 4/2 | 5/3 |

* Numerator=Number of fetuses affected; Denominator=Number of litters

affected.

** Positive control: 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 261 & 262; 267 through 270Date June 28, 1973Material FDA 71-53Laboratory No. 1575 q

Table 3-a
Summary of Soft Tissue Abnormalities
(Hamsters)

| Group | Material | Dose Level mg/kg | Dam | Number of Pups | Description |
|-------|-----------|---------------------|--------|-------------------|----------------------|
| 261 | Sham | 0.0 | S 5850 | 1 | Hepatocele |
| 262 | Aspirin* | 250.0 | A 5846 | 1 | Hydrocephalus |
| | | | A 5872 | 1 | Meningoencephalocele |
| 267 | FDA 71-53 | 6.5 | G 5004 | 1 | Umbilical hernia |
| | | | G 5024 | 1 | Hydrocephalus |
| 268 | FDA 71-53 | 30.2 | G 5054 | 1 | Hydrocephalus |
| 270 | FDA 71-53 | 650.0 | G 5101 | 1 | Hydrocephalus |

* Positive Control: 250.0 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 261 & 262, 267 through 270Date June 28, 1973Species HamstersLaboratory No. 1575 g

Table 4

Average Body Weights *

| Group | Material | Dose Level | 0 | 6 | 8 | 10 | 14** |
|-------|------------|------------|---------|-------|-------|-------|------------|
| | | mg/kg | Day --- | | | | |
| 261 | Sham | 0.0 | 119.6 | 124.3 | 117.4 | 127.7 | 154.9 (22) |
| 262 | Aspirin*** | 250.0 | 113.8 | 119.5 | 123.9 | 135.2 | 159.2 (22) |
| 267 | FDA 71-53 | 6.5 | 114.0 | 118.3 | 121.9 | 133.5 | 156.4 (26) |
| 268 | FDA 71-53 | 30.2 | 117.2 | 122.9 | 127.2 | 140.0 | 165.2 (22) |
| 269 | FDA 71-53 | 140.3 | 115.4 | 123.6 | 125.4 | 137.2 | 163.0 (24) |
| 270 | FDA 71-53 | 650.0 | 114.6 | 118.3 | 120.3 | 132.6 | 157.2 (24) |

* Of pregnant dams

** Number of surviving dams in parentheses (c.f. Table 1)

*** Positive control: 250.0 mg/kg



Appendix I

Teratology Study in Hamsters

Virgin adult female golden hamsters from an outbred strain were individually housed in mesh bottom cages in temperature and humidity controlled quarters with free access to food and fresh tap water at all times. They were mated (1 to 1) with mature males and the appearance of motile sperm in the vaginal smear was considered as Day 0 of gestation. Beginning on Day 6 and continuing daily through Day 10 of gestation, the indicated dose levels of the test material were administered by oral intubation. The controls were sham treated with the vehicle at a level equivalent to the group receiving the highest test dose. The test material was prepared and doses calculated according to the following table:

| Dosage (mg/kg) | Dose (ml/kg) | Concentration (mg/ml) |
|-------------------|-----------------|--------------------------|
| ≤ 250 | 1 | ≤ 250 |
| 251 - 500 | 2 | 125 - 250 |
| 501 - 750 | 3 | 133 - 250 |
| 751 - 1000 | 4 | 187 - 250 |
| 1001 - 1250 | 5 | 200 - 250 |
| 1251 - 1500 | 6 | 208 - 250 |
| 1501 - 1600 | 6.4 | 235 - 250 |

Body weights were recorded on Days 0, 6, 8, 10 and 14 of the gestation period. All animals were observed daily for appearance and behavior with particular attention to food consumption in order to better recognize any abnormalities resulting from anorexic effects in the pregnant animal.

On Day 14, all animals were subjected to Caesarian section under deep anesthesia and the numbers of implantation sites, resorption



sites, live and dead fetuses were recorded. All live pups were weighed and the genital tract of each dam was examined for any anatomical abnormalities.

All fetuses were examined grossly for the presence of external congenital defects, and one-third of each litter underwent detailed visceral examination employing the Wilson technique. The remaining two-thirds of the pups were cleared in potassium hydroxide, stained with alizarin red S dye, and examined for the presence of skeletal abnormalities.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 261Material ShamDose 0.0 mg/kgDate June 28, 1973Laboratory No. 1575

Appendix II

Reproduction Data in Hamsters (Individual)

| Dam No. | Fate* | Implant Sites | Fetuses | | Sex M | F | Resorption Sites | Average Fetus Weight (g) | Remarks |
|---------|-------|---------------|---------|------|----------|----|------------------|--------------------------|---------|
| | | | Alive | Dead | | | | | |
| S 5846 | P | 15 | 15 | | 8 | 7 | | 1.65 | |
| S 5847 | P | 12 | 11 | | 3 | 8 | 1 | 1.89 | |
| S 5848 | P | 14 | 12 | | 5 | 7 | 2 | 1.74 | |
| S 5849 | P | 14 | 14 | | 8 | 6 | | 1.87 | |
| S 5850 | P | 14 | 14 | | 5 | 9 | | 1.98 | |
| S 5851 | P | 13 | 13 | | 8 | 5 | | 1.85 | |
| S 5852 | P | 10 | 10 | | 3 | 7 | | 1.93 | |
| S 5853 | P | 15 | 15 | | 2 | 13 | | 1.78 | |
| S 5854 | P | 12 | 12 | | 4 | 8 | | 2.12 | |
| S 5855 | P | 15 | 15 | | 7 | 8 | | 1.76 | |
| S 5856 | NP | 0 | | | | | | --- | |
| S 5857 | P | 10 | 10 | | 4 | 6 | | 1.87 | |
| S 5858 | NP | 0 | | | 7 | 8 | | --- | |
| S 5859 | NP | 15 | 15 | | 5 | 8 | 1 | 1.61 | |
| S 5860 | P | 0 | | | 6 | 10 | | --- | |
| S 5861 | NP | 14 | 13 | | 6 | 10 | | 1.85 | |
| S 5862 | P | 16 | 16 | | 6 | 10 | | 1.53 | |
| S 5863 | P | 16 | 16 | | 6 | 10 | | 2.26 | |
| S 5864 | P | 13 | 13 | | 6 | 7 | | 1.56 | |
| S 5865 | P | 0 | | | 7 | 11 | 2 | 1.50 | |
| S 5866 | NP | 20 | 18 | | 16 | 12 | | --- | |
| S 5867 | P | 17 | 12 | | 6 | 7 | 1 | 2.19 | |
| S 5868 | P | 13 | 0 | | 6 | 7 | 1 | --- | |
| S 5869 | P | | | | | | | | |
| S 5870 | NP | | | | | | | | |
| S 5871 | | | | | | | | | |
| S 5872 | P | 14 | 14 | | 5 | 9 | | 1.69 | |
| S 5873 | P | 12 | 11 | | 4 | 7 | 1 | 1.51 | |
| S 5874 | | | | | | | | | |
| S 5875 | P | 14 | 14 | | 6 | 8 | | 1.61 | |

* P = Pregnant; NP = Not Pregnant

Not Assigned

Not Assigned

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 262Material AspirinDose 250.0 mg/kgDate June 28, 1973Laboratory No. 1575

Appendix II

Reproduction Data in Hamsters

(Individual)

| Dam No. | Fate* | Implant Sites | Fetuses | | Sex | | Resorption Sites | Average Fetus Weight (g) | Remarks |
|---------|-------|---------------|---------|------|-----|----|------------------|--------------------------|---------|
| | | | Alive | Dead | M | F | | | |
| A 5846 | P | 15 | 15 | | 6 | 9 | | 1.74 | |
| A 5847 | P | 11 | 11 | | 4 | 7 | | 1.63 | |
| A 5848 | P | 14 | 14 | | 8 | 6 | | 1.74 | |
| A 5849 | P | 15 | 14 | | 9 | 5 | 1 | 2.01 | |
| A 5850 | P | 13 | 13 | | 5 | 8 | | 2.00 | |
| A 5851 | P | 13 | 13 | | 5 | 8 | | 1.98 | |
| A 5852 | P | 10 | 10 | | 5 | 5 | | 1.80 | |
| A 5853 | P | 12 | 12 | | 7 | 5 | | 1.96 | |
| A 5854 | P | 16 | 16 | | 6 | 10 | | 1.86 | |
| A 5855 | P | 17 | 17 | | 5 | 12 | | 1.77 | |
| A 5856 | NP | 0 | 0 | | | | | ---- | |
| A 5857 | NP | 0 | 0 | | | | | ---- | |
| A 5858 | P | 15 | 15 | | 5 | 10 | | 1.86 | |
| A 5859 | P | 14 | 14 | | 4 | 10 | | 1.89 | |
| A 5860 | P | 13 | 13 | | 7 | 6 | | 1.90 | |
| A 5861 | P | 17 | 17 | | 5 | 12 | | 1.52 | |
| A 5862 | P | 12 | 11 | | 3 | 8 | 1 | 1.78 | |
| A 5863 | P | 12 | 11 | | 5 | 6 | 1 | 1.57 | |
| A 5864 | P | 13 | 13 | | 4 | 9 | | 1.67 | |
| A 5865 | P | 5 | 5 | | 2 | 3 | | 1.75 | |
| A 5866 | NP | 0 | 0 | | | | | ---- | |
| A 5867 | NP | 0 | 0 | | | | | ---- | |
| A 5868 | NP | 0 | 0 | | | | | ---- | |
| A 5869 | P | 20 | 20 | | 8 | 12 | | 1.54 | |
| A 5870 | P | 12 | 9 | | 4 | 5 | 3 | 1.93 | |
| A 5871 | P | 13 | 13 | | 5 | 8 | | 1.70 | |
| A 5872 | P | 16 | 16 | | 5 | 11 | | 1.91 | |

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 267Material FDA 71-53
Dose 6.5 mg/kgDate June 28, 1973Reproduction Data in Hamsters
(Individual)

Appendix II

Laboratory No. 1575 g

| Dam No. | Fate* | Implant Sites | Fetuses | | Sex M F | Resorption Sites | Average Fetus Weight (g) | Remarks |
|---------|-------|---------------|---------|------|---------------|---------------------|--------------------------|----------------------|
| | | | Alive | Dead | | | | |
| G 5001 | P | 15 | 15 | | 12 | 3 | 1.86 | |
| G 5002 | P | 12 | 11 | | 5 | 6 | 1.57 | |
| G 5003 | P | 15 | 14 | | 7 | 7 | 1.83 | |
| G 5004 | P | 14 | 14 | | 9 | 5 | 1.89 | |
| G 5005 | P | 12 | 11 | | 3 | 8 | 2.18 | |
| G 5006 | P | 12 | 12 | | 4 | 8 | 1.79 | |
| G 5007 | P | 12 | 12 | | 4 | 8 | 2.01 | |
| G 5008 | P | 15 | 15 | | 6 | 9 | 1.94 | |
| G 5009 | P | 12 | 12 | | 2 | 10 | 2.05 | |
| G 5010 | P | 13 | 13 | | 5 | 8 | 1.93 | |
| G 5011 | P | 11 | 11 | | 6 | 5 | 1.83 | |
| G 5012 | P | 13 | 13 | | 4 | 9 | 1.84 | |
| G 5013 | P | 14 | 14 | | — | — | — | Natural Birth Day 14 |
| G 5014 | P | 14 | 14 | | 6 | 8 | 1.95 | |
| G 5015 | P | 9 | 4 | 5 | 2 | 2 | 1.41 | |
| G 5016 | P | 17 | 17 | | 6 | 11 | 1.78 | |
| G 5017 | P | 11 | 10 | | 2 | 8 | 1.63 | |
| G 5018 | P | 10 | 8 | | 4 | 4 | 2.21 | |
| G 5019 | NP | 0 | 0 | | — | — | — | |
| G 5020 | P | 10 | 8 | | 3 | 5 | 2 | 1.60 |
| G 5021 | P | 17 | 15 | | 6 | 9 | 2 | 1.72 |
| G 5022 | NP | 0 | 0 | | — | — | — | |
| G 5023 | NP | 0 | 0 | | 5 | 9 | 1.39 | |
| G 5024 | P | 14 | 14 | | 4 | 10 | 1.55 | |
| G 5025 | P | 14 | 14 | | 2** | 9** | 2.00** | |
| G 5026 | P | 14 | 13 | | 4 | 8 | 1.83 | |
| G 5027 | P | 12 | 12 | | 5 | 10 | 1.84 | |
| G 5028 | P | 15 | 15 | | 6 | 7 | 1.71 | |
| G 5029 | P | 13 | 13 | | 7 | 9 | 1.80 | |
| G 5030 | P | 16 | 16 | | — | — | — | |

* P = Pregnant; NP = Not Pregnant

** Not all recorded.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 268Material FDA 71-53Dose 30.2 mg./kgDate June 28, 1973Laboratory No. 1575 g

Appendix II

Reproduction Data in Hamsters

(Individual)

Dam No. Fate*

Implant sites

Fetuses

Alive

Resorption Sites

Dead

M

F

Sex

M

F

Remarks

Weight (g)

| | | | | | | |
|--------|----|----|----|-------|-------|-------|
| G 5031 | P | 12 | 12 | 5 | 7 | 1.83 |
| G 5032 | P | 12 | 12 | 4 | 8 | 1.90 |
| G 5033 | P | 11 | 8 | 4 | 4 | 1.50 |
| G 5034 | P | 15 | 13 | 3 | 10 | 2.05 |
| G 5035 | P | 13 | 12 | 5 | 7 | 2.08 |
| G 5036 | NP | 0 | 0 | 3 | 10 | ----- |
| G 5037 | P | 13 | 13 | 5 | 9 | 1.87 |
| G 5038 | P | 14 | 14 | 5 | 9 | 1.84 |
| G 5039 | P | 15 | 14 | 5 | 9 | 1.75 |
| G 5040 | P | 17 | 17 | 6 | 11 | 1.75 |
| G 5041 | P | 13 | 13 | 7 | 6 | 1.74 |
| G 5042 | P | 15 | 15 | 6 | 9 | 1.97 |
| G 5043 | P | 16 | 16 | 5 | 11 | 1.98 |
| G 5044 | P | 19 | 19 | 8 | 11 | 1.74 |
| G 5045 | P | 9 | 8 | 4 | 4 | 2.07 |
| G 5046 | P | 12 | 12 | 3 | 9 | 1.74 |
| G 5047 | NP | 0 | 0 | ----- | ----- | ----- |
| G 5048 | P | 9 | 9 | 7 | 11 | 1.75 |
| G 5049 | P | 18 | 18 | 6 | 6 | 2.17 |
| G 5050 | P | 12 | 12 | 7 | 10 | 1.64 |
| G 5051 | P | 17 | 17 | 5 | 12 | 1.51 |
| G 5052 | P | 17 | 17 | 1 | 6 | 1.53 |
| G 5053 | P | 17 | 16 | 16 | 7 | 1.97 |
| G 5054 | P | 16 | 16 | 9 | 3 | 1.62 |
| G 5055 | P | 9 | 9 | 6 | 6 | ----- |

Natural Birth Day 14

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 269Material FDA 71-53Dose 140.3 mg/kgDate June 28, 1973
Laboratory No. 1575 g

Appendix II

Reproduction Data in Hamsters (Individual)

| Dam No. | Fate* | Implant Sites | Fetuses | | Sex | | Resorption Sites | Average Fetus Weight (g) | Remarks |
|---------|-------|---------------|---------|------|-----|----|------------------|--------------------------|---------|
| | | | Alive | Dead | M | F | | | |
| G 5061 | P | 11 | 9 | | 3 | 6 | 2 | 1.77 | |
| G 5062 | P | 15 | 14 | | 5 | 9 | 1 | 1.75 | |
| G 5063 | P | 14 | 14 | | 6 | 8 | | 1.76 | |
| G 5064 | P | 9 | 9 | | 5 | 4 | | 1.79 | |
| G 5065 | P | 12 | 12 | | 5 | 7 | | 1.74 | |
| G 5066 | NP | 0 | | | | | | ----- | |
| G 5067 | P | 13 | 13 | | 5 | 8 | 1 | 2.17 | |
| G 5068 | P | 11 | 10 | | 3 | 7 | | 1.74 | |
| G 5069 | P | 12 | 12 | | 3 | 9 | | 2.28 | |
| G 5070 | P | 12 | 11 | | 4 | 7 | 1 | 1.95 | |
| G 5071 | P | 13 | 13 | | 4 | 9 | | 1.93 | |
| G 5072 | P | 11 | 11 | | 2 | 9 | | 1.78 | |
| G 5073 | P | 10 | 10 | | 3 | 7 | | 1.76 | |
| G 5074 | P | 12 | 12 | | 4 | 8 | | 1.93 | |
| G 5075 | P | 14 | 14 | | 6 | 8 | | 2.18 | |
| G 5076 | P | 14 | 14 | | 4 | 10 | | 1.94 | |
| G 5077 | P | 13 | 13 | | 4 | 9 | | 2.02 | |
| G 5078 | P | 12 | 12 | | 5 | 7 | | 2.31 | |
| G 5079 | P | 16 | 16 | | 6 | 10 | | 1.67 | |
| G 5080 | P | 11 | 11 | | 5 | 6 | | 2.23 | |
| G 5081 | P | 17 | 16 | 1 | 5 | 11 | | 1.75 | |
| G 5082 | P | 17 | 17 | | 8 | 9 | | 1.66 | |
| G 5083 | P | 15 | 15 | | 5 | 10 | | 1.78 | |
| G 5084 | P | 12 | 12 | | 6 | 6 | | 2.43 | |
| G 5085 | P | 15 | 14 | | 10 | 4 | 1 | 1.86 | |

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 270Material FDA 71-53
Dose 650.0 mg/kgDate June 28, 1973Laboratory No. 1575 g

Appendix II

Reproduction Data in Hamsters

(Individual)

Dam No. Fate*

Implant Sites Fetuses Sex
 Alive Dead M F
G 5091 P 16 16 7 9 1.83
G 5092 P 14 14 6 8 2.01
G 5093 P 11 11 4 7 2.03
G 5094 P 13 13 4 9 1.88
G 5095 P 12 11 7 4 1.98
G 5096 P 14 14 7 7 1.06
G 5097 P 11 11 4 7 1.84
G 5098 P 15 15 7 8 1.98
G 5099 NP 0 0 3 10 2.04
G 5100 P 16 13 3 10 1.72
G 5101 P 15 14 4 10 1.85
G 5102 P 12 12 4 8 1.77
G 5103 P 13 13 6 7 1.82
G 5104 P 11 11 4 7 1.82
G 5105 NP 0 0 4 6 2.13
G 5106 P 10 10 4 6 2.13
G 5107 NP 0 0 4 6 1.95
G 5108 NP 0 0 6 9 1.73
G 5109 NP 0 0 5 8 1.90
G 5110 P 13 10 7 6 1.79
G 5111 P 15 15 5 8 1.83
G 5112 P 15 13 1 5 1.78
G 5113 P 13 13 7 6 1.80
G 5114 P 18 18 9 9 1.70
G 5115 P 19 19 11 8 1.72
G 5116 P 11 11 3 8 1.90
G 5117 P 14 14 3 11 1.90
G 5118 P 13 13 5 8 1.90
G 5119 P 15 15 7 8 1.90Remarks
Average Fetus Weight (g)

* P = Pregnant; NP = Not Pregnant

STREIBER

FROM



#33

FOOD AND DRUG
Research LABORATORIES, INC.

ROUTE 17 (P.O. BOX 107)
WAVERLY, NEW YORK 14892

FINAL

September 17, 1973

Teratologic Evaluation of FDA 71-53

(Agar Agar)

IN

Rabbits

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**F I N A L
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**WAVERLY DIVISION
Route 17
P.O. Box 107
Waverly, New York 14892
(607) 565-2931**

Submitted to: DHEW/Public Health Service **Date** September 17, 1973
Food and Drug Administration CA-272
5600 Fishers Lane-Room 5C-13
Rockville, Maryland 20852

Laboratory No. 1576 g
Contract No. FDA 71-260

Sample: Fine tan powdered material

Marking: FDA 71-53 (Agar Agar)

Examination Requested: Teratologic evaluation of FDA 71-53 in rabbits

Procedure: (See Appendix I)

Results: See Tables 1 through 4 and Appendix II

Conclusion: On the basis of the data presented herein, the following conclusion appears to be warranted:

"The administration of up to 118.5 mg/kg (body weight) of the test material to pregnant rabbits for 13 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls.

However, at the highest level of administration (400.0 mg/kg) there was a significant increase in mortality among treated dams and a decrease in the pregnancy rate of survivors. All other parameters were normal.

It is the opinion of the investigator that the administration of what amounts to essentially an LD₅₀ dose (even though distributed over a 13-day period) had resulted in a predictable effect on the pregnant animal, but no teratologic effect on this species."

FOOD and DRUG RESEARCH LABORATORIES, INC.

Kenneth Morgareidge
Kenneth Morgareidge Ph.D.
Vice President

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 261 & 262; 267 through 270Material: FDA 71-53Date: August 15, 1973
Laboratory No.: 1576 g

Table 1

Fate Summary
(Rabbits)

| Group | Material | Dose** mg/kg | Mated | Total | Surviving at Term | |
|-------|-----------|-----------------|-------|-------|-------------------|----------------|
| | | | | | Pregnant | Total Pregnant |
| 261 | Sham | 0.0 | 21 | 12 | 18 | 10 |
| 262 | 6-AN* | 2.5 | 18 | 10 | 17 | 9 |
| 267 | FDA 71-53 | 5.5 | 17 | 14 | 14 | 12 |
| 268 | FDA 71-53 | 25.6 | 15 | 12 | 14 | 11 |
| 269 | FDA 71-53 | 118.5 | 15 | 12 | 15 | 12 |
| 270 | FDA 71-53 | 400.0 | 25 | 20 | 16 | 14 |

* Positive Control: 2.5 mg/kg of 6-aminonicotinamide dosed on Day 9

** Administered as a corn oil suspension (See Appendix I)

1) Includes all dams examined at term

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group : 261 & 262, 267 through 270
 Material : FDA 71-53

Date : August 15, 1973
 Laboratory No. : 1576 g

Table 2
 Reproduction Data
 (Rabbits)

| Group : | 261 | 262 | 267 | 268 | 269 | 270 |
|------------------------------------|------|--------|------|------|-------|-------|
| Dose (mg/kg) : | Sham | 6-AN** | 5.5 | 25.6 | 118.5 | 400.0 |
| Pregnancies | | | | | | |
| Total No. | 12 | 10 | 14 | 12 | 12 | 20 |
| Died or Aborted (before Day 29) | 2 | 1 | 2 | 1 | 0 | 6 |
| To term (on Day 29) | 10 | 9 | 12 | 11 | 12 | 14 |
| Corpora Lutea | | | | | | |
| Total No. | 222 | 133 | 231 | 195 | 189 | 324 |
| Average/dam mated | 14.8 | 8.87 | 13.6 | 13.0 | 12.6 | 13.0 |
| Live Litters | | | | | | |
| Total No.* | 9 | 7 | 10 | 11 | 12 | 13 |
| Implant Sites | | | | | | |
| Total No. | 67 | 43 | 78 | 66 | 55 | 82 |
| Average/dam* | 6.70 | 4.78 | 6.50 | 6.00 | 4.58 | 5.86 |
| Resorptions | | | | | | |
| Total No.* | 11 | 14 | 5 | 3 | 3 | 3 |
| Dams with 1 or more sites resorbed | 5 | 6 | 3 | 3 | 1 | 2 |
| Dams with all sites resorbed | 1 | 2 | 1 | -- | -- | -- |
| Per cent partial resorptions | 50.0 | 66.7 | 25.0 | 27.3 | 8.33 | 14.3 |
| Per cent complete resorptions | 10.0 | 22.2 | 8.33 | -- | -- | -- |
| Live Fetus | | | | | | |
| Total No. | 54 | 28 | 64 | 63 | 52 | 74 |
| Average/dam* | 5.40 | 3.11 | 5.33 | 5.73 | 4.33 | 5.29 |
| Sex ratio (M/F) | 0.93 | 0.87 | 1.00 | 1.42 | 0.73 | 0.95 |
| Dead Fetus | | | | | | |
| Total No.* | 2 | 1 | 9 | -- | -- | 5 |
| Dams with 1 or more dead | 2 | 1 | 2 | -- | -- | 3 |
| Dams with all dead | -- | -- | -- | -- | -- | 1 |
| Per cent partial dead | 20.0 | 11.1 | 16.7 | -- | -- | 21.4 |
| Per cent all dead | -- | -- | -- | -- | -- | 7.14 |
| Average Fetus Weight, g | 38.2 | 33.2 | 36.4 | 38.9 | 44.1 | 39.8 |

* Includes only those dams examined at term.

** Positive Control: 2.5 mg/kg of 6-aminonicotinamide dosed on Day 9

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 261 & 262; 267 through 270Laboratory No. 1576 g

Table 3

Material FDA 71-53Date August 15, 1973Summary of Skeletal Findings*
(Rabbits)

| Findings | Group No.: | 261 | 262 | 267 | 268 | 269 | 270 |
|------------------------------------|---------------|------|--------|-------|-------|-------|-------|
| | Dose (mg/kg): | Sham | 6-AN** | 5.5 | 25.6 | 118.5 | 400.0 |
| Live Fetuses Examined (at term) | | 54/9 | 28/7 | 64/10 | 63/11 | 52/12 | 74/13 |
| Sternebrae | | | | | | | |
| Incomplete oss. | | 10/4 | 3/3 | 1/1 | 1/1 | | 4/2 |
| Scrambled | | | 1/1 | | | | |
| Bipartite | | 1/1 | 1/1 | | | | 1/1 |
| Fused | | | 1/1 | | | | |
| Extra | | 1/1 | 2/2 | 2/1 | 2/2 | 1/1 | 1/1 |
| Missing | | 3/3 | | | | | 1/1 |
| Other | | | | | | | |
| Ribs | | | | | | | |
| Incomplete oss. | | | | | | | |
| Fused/split | | | 14/5 | | | | |
| Wavy | | | 1/1 | | | | |
| Less than 12 | | | | | | | |
| More than 13 | | | | | | | |
| Other | | | | | | | |
| Vertebrae | | | | | | | |
| Incomplete oss. | | | 2/1 | | | | |
| Scrambled | | | 16/5 | | | | |
| Fused | | | 3/1 | | | | |
| Extra ctrs. oss. | | | | | | | |
| Scoliosis | | | 1/1 | | | | |
| Tail defects | | | 26/7 | | | | |
| Other | | | | | | | |
| Skull | | | | | | | |
| Incomplete closure | | | | | | | |
| Missing | | | | | | 1/1 | |
| Craniostosis | | | | | | | |
| Other | | | | | | 1/1 | |
| Extremities | | | | | | | |
| Incomplete oss. | | | | | | | 1/1 |
| Missing | | | | | | | |
| Extra | | | | | | | |
| Miscellaneous | | | | | | | |

* Numerator=Number of fetuses affected; Denominator=Number of litters

** Positive control: 2.5 mg/kg of 6-aminonicotinamide dosed on Day 9 affected.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 261 & 262; 267 through 270Date August 15, 1973Material FDA 71-53Laboratory No. 1576 g

Table 3-a
Summary of Soft Tissue Abnormalities
(Rabbits)

| Group | Material | Dose Level mg/kg | Dam | Number of Pups | Description |
|-------|-----------|---------------------|--------|-------------------|---|
| 261 | Sham | 0.0 | S 6436 | 1 | Umbilical hernia |
| 262 | 6-AN** | 2.5 | Z 6442 | 1 | Medial rotation of hind limbs |
| | | | Z 6444 | 1 | Medial rotation of hind limbs |
| | | | Z 6445 | 1 | Medial rotation of hind limbs |
| | | | Z 6446 | 1 | Runt; anopia; medial rotation of hind limbs |
| | | | | 1 | Anopia; medial rotation of hind limbs |
| | | | | 1 | Anopia |
| | | | Z 6447 | 3 | Anopia |
| | | | Z 6451 | 6 | Anopia |
| | | | | 1 | Runt; anopia |
| 268 | FDA 71-53 | 25.6 | G 6027 | 1 | Fetal monster |
| 270 | FDA 71-53 | 400.0 | G 6073 | 1 | Short tail |

* Positive Control: 2.5 mg/kg of 6-aminonicotinamide dosed on Day 9

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 261 & 262; 267 through 270Date August 15, 1973Species RabbitsLaboratory No. 1576 q

Table 4

Average Body Weights*

| Group | Material | Dose Level | Day-- | | | | |
|-------|-----------|------------|-------|------|------|------|-----------|
| | | | 0 | 6 | 12 | 18 | |
| | | mg/kg | kg-- | | | | |
| 261 | Sham | 0.0 | 2.60 | 2.62 | 2.62 | 2.95 | 2.78 (10) |
| 262 | 6-AN*** | 2.5 | 2.49 | 2.56 | 2.55 | 2.60 | 2.70 (9) |
| 267 | FDA 71-53 | 5.5 | 2.40 | 2.54 | 2.55 | 2.50 | 2.70 (12) |
| 268 | FDA 71-53 | 25.6 | 2.39 | 2.47 | 2.48 | 2.51 | 2.61 (11) |
| 269 | FDA 71-53 | 118.5 | 2.42 | 2.53 | 2.52 | 2.57 | 2.69 (12) |
| 270 | FDA 71-53 | 400.0 | 2.44 | 2.50 | 2.53 | 2.51 | 2.63 (14) |

* Of pregnant dams

** Number of surviving dams in parentheses (c.f. Table 1)

*** Positive control: 2.5 mg/kg of 6-aminonicotinamide dosed on Day 9



Appendix I

Teratology Study in Rabbits

Virgin, adult, Dutch-belted female rabbits were individually housed in mesh bottom cages in temperature and humidity-controlled quarters with free access to food and fresh tap water. On Day 0, each doe was given an injection of 0.4 ml of human chorionic gonadotropin (400 IU) via the marginal ear vein. Three hours later, each doe was inseminated artificially with 0.3 ml of diluted semen from a proven donor buck using approximately 20×10^6 motile sperm according to the procedure described by Vogen et al (Pharmacologist 11, 282 (1969)). Beginning on Day 6 and continuing daily through Day 18 the females were dosed with the indicated dosages by oral intubation. The controls were sham treated with the vehicle at a level equivalent to the group receiving the highest test dose. The test material was prepared and doses calculated according to the following table:

| Dosage (mg/kg) | Dose (ml/kg) | Concentration (mg/ml) |
|-------------------|-----------------|--------------------------|
| ≤ 250 | 1 | ≤ 250 |
| 251 - 500 | 2 | 125 - 250 |
| 501 - 750 | 3 | 133 - 250 |
| 751 - 1000 | 4 | 187 - 250 |
| 1001 - 1250 | 5 | 200 - 250 |
| 1251 - 1500 | 6 | 208 - 250 |
| 1501 - 1600 | 6.4 | 235 - 250 |

Body weights were recorded on Days 0, 6, 12, 18, and 29 of gestation. All animals were observed daily for appearance and behavior, with particular attention to food consumption and body weight in order to rule out any abnormalities which may have occurred as a result of anorexic effects in the pregnant female animal.



On Day 29 all does were subjected to Caesarean section under surgical anesthesia, and the numbers of corpora lutea, implantation sites, resorption sites and live and dead fetuses were recorded. Body weights of the live pups were also recorded. The urogenital tract of each animal was examined in detail for normality. In addition all fetuses underwent a detailed gross examination for the presence of external congenital abnormalities. The live fetuses of each litter were then placed in an incubator for 24 hours for the evaluation of neonatal survival. All surviving pups were sacrificed, and all pups examined for visceral abnormalities (by dissection). All fetuses were then cleared in potassium hydroxide (KOH), stained with alizarin red S dye and examined for skeletal defects.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 261Material ShamDose 0.0 mg/kgDate August 15, 1973Laboratory No. 1576

Appendix II

Reproduction Data in Rabbits
(Individual)

| Dam No. | Fate* | Corpora Lutea | Implant Sites | Fetuses | | Sex M F | Resorption Sites | Average Fetus Weight (g) | Remarks |
|---------|-------|---------------|---------------|---------|------|---------------|---------------------|--------------------------|-----------------------|
| | | | | Alive | Dead | | | | |
| S 6431 | P | 10 | 5 | 4 | | 2 | 2 | 1 | 33.8 |
| S 6432 | NP | 0 | 0 | | | | | | ----- |
| S 6433 | NP | 18 | 0 | | | | | | Died Day 21 |
| S 6434 | P | 15 | 6 | -- | | | | | Died Day 26 |
| S 6435 | P | 16 | 8 | 7 | 1 | 3 | 4 | | 40.4 |
| S 6436 | P | 18 | 9 | 2 | 1 | 1 | 1 | 6 | 31.0 |
| S 6437 | NP | 0 | 0 | | | | | | One Neonatal Death |
| S 6438 | P | 15 | 7 | 7 | | 5 | 2 | | 39.6 |
| S 6439 | P | 16 | 12 | -- | | | | | Died Day 10 |
| S 6440 | P | 17 | 3 | 2 | | 0 | 2 | 1 | 51.5 |
| S 6446 | P | 36 | 8 | 8 | | 3 | 5 | | 23.1 |
| S 6447 | NP | --** | 0 | | | | | | Three Neonatal Deaths |
| S 6448 | P | 12 | 2 | | | | | | ----- |
| S 6449 | P | 15 | 11 | 10 | 5 | | | | ----- |
| S 6450 | P | 21 | 5 | | | | | | ----- |
| S 6451 | NP | --** | 0 | | | | | | ----- |
| S 6452 | NP | --** | 0 | | | | | | ----- |
| S 6453 | NP | --** | 0 | | | | | | ----- |
| S 6454 | NP | --** | 0 | | | | | | ----- |
| S 6455 | NP | --** | 0 | | | | | | ----- |
| S 6476 | P | 13 | 9 | 9 | | 3 | 6 | | 38.2 |

* P = Pregnant; NP = Not Pregnant
 ** Not Recorded

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 262
 Material 6-AN
 Dose 2.5 mg/kg

Date August 15, 1973
 Laboratory No. 1576

Appendix II

Reproduction Data in Rabbits (Individual)

| Dam No. | Fate* | Corpora Lutea | Implant Sites | Fetuses | | Sex M F | Resorption Sites | Average Fetus Weight (g) | Remarks |
|---------|-------|---------------|---------------|---------|------|-----------------|------------------|--------------------------|-----------------------|
| | | | | Alive | Dead | | | | |
| Z 6431 | P | 13 | 1 | | | | | | Died Day 1 |
| Z 6436 | NP | 0 | 0 | | | | | | ----- |
| Z 6437 | NP | 0 | 0 | | | | | | ----- |
| Z 6441 | NP | 0 | 0 | 2 | | 1 1 | | 35.9 | One Neonatal Death |
| Z 6442 | P | 9 | | 4 | | 0 4 | | 34.8 | Two Neonatal Deaths |
| Z 6443 | P | 12 | 4 | 4 | | 1 3 | | 34.2 | Two Neonatal Deaths |
| Z 6444 | P | 15 | 6 | 4 | | 4 2 | | 27.5 | Six Neonatal Deaths |
| Z 6445 | P | 13 | 9 | 6 | | 1 2 | | 26.7 | Three Neonatal Deaths |
| Z 6446 | P | 12 | 6 | 3 | | 1 2 | | 40.5 | |
| Z 6447 | P | 26 | 4 | 3 | | 2 1 | 1 | | |
| Z 6448 | NP | 0 | 0 | | | | | | ----- |
| Z 6449 | P | 11 | 1 | | | | 1 | | ----- |
| Z 6450 | NP | 0 | 0 | | | | | 32.6 | One Neonatal Death |
| Z 6451 | P | 13 | 7 | 6 | | 1 4 | 2 | | |
| Z 6452 | P | 9 | 4 | | | | 4 | | ----- |
| Z 6453 | NP | | | 0 | | | 0 | | ----- |
| Z 6454 | NP | | | 0 | | | 0 | | ----- |
| Z 6455 | NP | | | | | | | | |

* P = Pregnant; NP = Not Pregnant
 ** Not Recorded

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 267

Material FDA 71-53

Dose 5.5 mg/kgDate August 15, 1973Laboratory No. 1576 q

Appendix II

Reproduction Data in Rabbits

(Individual)

| Dam No. | Fate* | Corpora Lutea | Implant Sites | Fetuses Alive | Fetuses Dead | Sex M | Sex F | Resorption Sites | Average Fetus Weight (g) | Remarks |
|---------|-------|---------------|---------------|---------------|--------------|-------|-------|------------------|--------------------------|---------------------|
| G 6001 | NP | 13 | 0 | | | 3 | 3 | | | Died Day 8 |
| G 6002 | P | 19 | 7 | 6 | 1 | 3 | 3 | | 22.2 | |
| G 6003 | NP | 0 | 0 | | | | | | | |
| G 6004 | P | 11 | 7 | | | | | 7 | | Died Day 12 |
| G 6005 | P | 14 | 10 | 10 | | 7 | 3 | | 33.5 | One Neonatal Death |
| G 6006 | P | 22 | 2 | -- | | -- | 1 | | | Died Day 20 |
| G 6007 | P | 13 | 7 | 7 | | 5 | 2 | | 37.5 | |
| G 6008 | P | 13 | 6 | 6 | | 3 | 3 | | 36.3 | |
| G 6009 | P | 15 | 4 | 4 | | 2 | 2 | | 38.8 | |
| G 6010 | P | 16 | 7 | 6 | | 2 | 4 | 1 | 42.7 | |
| G 6011 | P | 17 | 5 | 5 | | 2 | 3 | | 37.3 | |
| G 6012 | NP | 3 | 0 | | | | | | | |
| G 6013 | P | 17 | 7 | 7 | | 3 | 4 | | 30.9 | |
| G 6014 | P | 11 | 5 | 5 | | 1 | 4 | | 47.9 | |
| G 6015 | P | 20 | 2 | | | | | 2 | | |
| G 6021 | P | 16 | 10 | | | | | 2 | | Ten Neonatal Deaths |
| G 6022 | P | 11 | 8 | | | | | 4 | 36.8 | |

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 268

Material FDA 71-53

Dose 25.6 mg/kgDate August 15, 1973Laboratory No. 1576 g

Appendix II

Reproduction Data in Rabbits

(Individual)

| Dam No. | Fate* | Corpora Lutea | Implant Sites | Fetuses Alive | Fetuses Dead | M | F | Resorption Sites | Average Fetus Weight (g) | Remarks |
|---------|-------|---------------|---------------|---------------|--------------|---|---|------------------|--------------------------|------------------------------------|
| G 6021 | P | 11 | 4 | | | 3 | 1 | | 39.8 | |
| G 6022 | P | 17 | 5 | | | 3 | 2 | | 46.7 | One Neonatal Death |
| G 6023 | P | 15 | 11 | | | 4 | 7 | | 31.7 | |
| G 6024 | NP | 0 | 0 | | | | | | ---- | |
| G 6025 | P | 7 | 4 | | | 2 | 2 | | 39.9 | |
| G 6026 | P | 7 | 4 | | | | | | ---- | |
| G 6027 | P | 17 | 3 | 2 | | 1 | 1 | 1 | 39.8 | Died Day 27 One Neonatal Deaths |
| G 6028 | NP | 15 | 0 | | | | | | ---- | |
| G 6029 | NP | 15 | 0 | | | | | | ---- | |
| G 6030 | P | 13 | 10 | | | 5 | 5 | | 30.4 | |
| G 6031 | P | 11 | 8 | | | 5 | 3 | | 33.5 | |
| G 6032 | P | 19 | 9 | | | 7 | 2 | | 36.7 | |
| G 6033 | P | 9 | 2 | | | 1 | 1 | | 48.1 | |
| G 6034 | P | 20 | 8 | | | 6 | 1 | 1 | 40.2 | |
| G 6035 | P | 19 | 2 | | | 0 | 1 | 1 | 41.3 | |

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 269

Material FDA 71-53

Dose 118.5 mg/kgDate August 15, 1973Laboratory No. 1576 q

Appendix II

Reproduction Data in Rabbits (Individual)

| Dam No. | Fate* | Corpora Lutea | Implant Sites | Fetuses | | Sex M F | Resorption Sites | Average Fetus Weight (g) | Remarks |
|---------|-------|---------------|---------------|---------|------|---------------|---------------------|--------------------------|---------------------|
| | | | | Alive | Dead | | | | |
| G 6041 | P | 14 | 6 | 3 | | 1 | 2 | 3 | 45.0 |
| G 6042 | P | 16 | 5 | 5 | | 3 | 2 | | 34.7 |
| G 6043 | NP | 0 | 0 | | | | | | ---- |
| G 6044 | P | 17 | 10 | 10 | | 3 | 7 | | 34.4 |
| G 6045 | P | 12 | 6 | 6 | | 2 | 4 | | One Neonatal Deaths |
| G 6046 | P | 15 | 2 | 2 | | 0 | 2 | | 42.3 |
| G 6047 | P | 18 | 6 | 6 | | 3 | 3 | | 56.5 |
| G 6048 | P | 18 | 2 | 2 | | 0 | 2 | | 44.5 |
| G 6049 | P | 29 | 5 | 5 | | 2 | 3 | | 54.6 |
| G 6050 | P | 14 | 3 | 3 | | 1 | 2 | | 46.2 |
| G 6051 | NP | 0 | 0 | | | | | | 43.5 |
| G 6052 | P | 12 | 1 | 1 | | 0 | 1 | | 46.8 |
| G 6053 | NP | 0 | 0 | | | | | | ---- |
| G 6054 | P | 9 | 5 | 5 | | 5 | 0 | | 41.1 |
| G 6055 | P | 15 | 4 | 4 | | 2 | 2 | | 39.8 |

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 270

Material FDA 71-53

Dose 400.0 mg/kgDate August 15, 1973Laboratory No. 15769

Appendix II

Reproduction Data in Rabbits

(Individual)

| Dam No. | Fate* | Corpora Lutea | Implant Sites | Fetuses | | Sex M F | Resorption Sites | Average Fetus Weight (g) | Remarks |
|---------|-------|---------------|---------------|---------|------|-----------------|---------------------|-----------------------------|--------------------|
| | | | | Alive | Dead | | | | |
| G 6061 | NP | 15 | 0 | | | | | | Died Day 8 |
| G 6062 | P | 9 | 8 | | | | | | Died Day 10 |
| G 6063 | P | 13 | 10 | -- | -- | | | | Died Day 17 |
| G 6064 | P | 11 | 6 | | | 3 | 3 | 32.2 | |
| G 6065 | P | 11 | 5 | | | 4 | 1 | 39.3 | |
| G 6066 | NP | 0 | 0 | | | | | | |
| G 6067 | P | 9 | 5 | | | | | | Died Day 13 |
| G 6068 | P | 10 | 9 | -- | -- | | | | Died Day 12 |
| G 6069 | P | 10 | 6 | | | | | | Died Day 13 |
| G 6070 | NP | 25 | 0 | | | | | | Died Day 14 |
| G 6071 | P | 12 | 9 | -- | -- | | | | Died Day 9 |
| G 6072 | NP | 8 | 0 | | | | | | Died Day 9 |
| G 6073 | P | 10 | 8 | 2 | 2 | 6 | 1 | 32.3 | One Neonatal Death |
| G 6074 | P | 53 | 2 | 2 | 1 | 1 | | 54.2 | |
| G 6075 | NP | 0 | 0 | | | | | | |
| G 6076 | P | 17 | 4 | 4 | 1 | 3 | | 40.2 | |
| G 6077 | P | 12 | 6 | 6 | 3 | 3 | | 45.8 | |
| G 6078 | P | 11 | 3 | 2 | 1 | 0 | 2 | 41.7 | |
| G 6080 | P | 17 | 6 | 6 | 4 | 2 | | 36.2 | |
| G 6082 | P | 8 | 2 | | | | | | |
| G 6083 | P | 16 | 11 | 10 | 4 | 6 | 1 | 32.3 | |
| G 6084 | P | 12 | 7 | | | 4 | 3 | 41.2 | |
| G 6085 | P | 11 | 6 | | | 3 | 3 | 35.6 | |
| G 6087 | P | 10 | 7 | | | 4 | 3 | 40.2 | |
| G 6088 | P | 14 | 7 | | | 3 | 2 | 45.8 | |

* P = Pregnant; NP = Not Pregnant